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The Seventh Conference
The CareFusion Center for Safety and Clinical Excellence
June 7-8, 2007, San Diego, CA
Philip J. Schneider, MS, FASHP, Editor*

Intensive Insulin Therapy for Tight Glycemic Control

**Research
Therapy
Monitoring
Nursing**

International Conference on Intensive Insulin Therapy for Tight Glycemic Control

The seventh invitational conference at the CareFusion Center for Safety and Clinical Excellence in San Diego, held June 7-8, 2007, brought together a distinguished faculty from clinical practice, academia, and organizations. Judith Jacobi, PharmD, FCCM, FCCP, BCPS, Critical Care Pharmacist, Methodist Hospital/Clarian Health, Indianapolis, IN and Timothy S. Bailey, MD, FACE, CPI, Advanced Metabolic Care and Research, Escondido, CA chaired the conference. Internationally recognized experts on research, current issues and opportunities in the use of intensive insulin therapy for tight glycemic control (TGC IIT) presented.

This conference report summarizes the information presented on TGC IIT with regard to research findings, safety concerns, emerging practices, monitoring, and nursing issues as researchers and clinicians seek to optimize insulin therapy to help maintain normoglycemia in critically ill patients. The proceedings were edited by Philip J. Schneider, MS, FASHP, Clinical Professor and Director, Latiolais Leadership Program, College of Pharmacy, The Ohio State University, Columbus, OH.

Content

Introduction

- p3 Tight Glycemic Control: An Overview
Judith Jacobi, PharmD, FCCM, FCCP, BCPS
 Methodist Hospital/Clarian Health, Indianapolis, IN
Timothy S. Bailey, MD, FACE, CPI
 Advanced Metabolic Care and Research
 Escondido, CA

Research

- p4 A Brief History of Tight Glycemic Control: What We Know in 2007; and How We Got Here
Tony Furnary, MD
 Starr-Wood Cardiac Group, Portland, OR
- p10 Intensive Insulin Therapy and the NICE-SUGAR Study
Simon Finfer, MBBS
 Royal North Shore Hospital of Sydney, Australia
- p13 European Multi-center Trials with Tight Glucose Control by Intensive Insulin Therapy
Philippe Devos, MD
 The George Institute of Liege, Belgium
- p17 Implementation of Tight Glycemic Control at Stamford Hospital
James Krinsley, MD
 Stamford Hospital, Stamford, CT
- p21 Meta-analysis of Randomized Trials of Tight Glycemic Control
Anastassios G. Pittas, MD, MS
 Tufts/New England Medical Center, Boston, MA
- p23 Perioperative Glucose Management and IIT in The Operating Room
Richard Prielipp, MD
 University of Minnesota, Minneapolis, MN
Douglas Coursin, MD
 University of Wisconsin, Madison, WI
- p26 Economic Advantages of Tight Glycemic Control
Judi Jacobi, PharmD
 Methodist Hospital/Clarian Health, Indianapolis, IN

Therapy

- p29 Intensive Insulin Therapy in the Intensive Care Unit
Robert Osburne, MD
 Atlanta Medical Center, Atlanta, GA
- p33 Use of Computerized Algorithm in Patients Undergoing Cardiovascular Surgery: A Protocol for Tight Glycemic Control
Bruce Bode, MD
 Atlanta Diabetes Associates, Atlanta, GA
- p36 Computerized Management of Tight Glycemic Control
Pat Burgess, MD, PhD
 Carolinas Medical Center, Charlotte, NC
- p39 Analysis of Variation in Insulin Protocols
Guy Soo Hoo, MD
 VA Hospital, Los Angeles, CA
- p43 Improving ICU Quality and Safety: Implications for Tight Glycemic Control
Sean Berenholtz, MD
 Johns Hopkins, Baltimore, MD
- p47 Specialized Nutrition Support and Glycemic Control
Kalman Holdy, MD
 Sharp Healthcare, San Diego, CA

p50	Examining Medication Errors Associated with Intravenous Insulin	<i>John Santell, MS</i> US Pharmacopeia, Washington, DC
p53	The Portland-Vancouver Regional Inpatient Glycemic Control Collaborative	<i>Chris Hogness, MD, MPH</i> Southwest Washington Medical Center Vancouver, WA
p56	Building Transitions from the ICU to the Ward for the Hyperglycemic Patient: One Piece of the Puzzle	<i>Greg Maynard, MD</i> UCSD, San Diego, CA

Monitoring

p59	Glucose Control and (Continuous) Glucose Monitoring in Critical Illness	<i>Christophe De Block, MD</i> Antwerp University Hospital, Belgium
p62	Glucose Sensor Technology: Current State and Future Trends	<i>Timothy Bailey, MD</i> Advanced Metabolic Care and Research Escondido, CA
p64	Assessing the Accuracy and Confounding Factors in Critical Care Glucose Monitoring	<i>Nam Tran, PhD (Candidate)</i> UC Davis, Davis, CA
p68	Glucose Sensor Augmented Insulin Delivery in the Hospital: Open and Closed-Loop Methods	<i>Jeffrey Joseph, DO</i> T. Jefferson University, Philadelphia, PA

Nursing

p73	The Impact of Intensive Insulin Therapy on Nursing	<i>Daleen Aragon, PhD, CCRN, FCCM</i> Orlando Regional, Orlando, FL
p76	Nursing Education and Intensive Insulin Therapy	<i>Carol Manchester, MSN, APRN, BC-ADM, CDE</i> University of Minnesota, Minneapolis, MN
p79	Applying Glucometrics to Tight Glycemic Control	<i>Jacqueline Thompson, MAS, RN, CDE</i> Sharp Healthcare, San Diego, CA

Roundtable

p81	Impact on Hospital Costs
p81	Reasonable Target
p82	Factors that Complicate Glycemic Control
p82	Administrative Aspects of IIT
p83	Risk of Hypoglycemia
p84	Blood Glucose Measurement

Appendix

p85	Table. Major Published Randomized Controlled Trials with Insulin Therapy in Critically Ill Patients	<i>Anastassios G. Pittas, MD, MS</i> Tufts/New England Medical Center, Boston, MA
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Tight Glycemic Control: An Overview

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More than five years ago the publication of a landmark trial of intensive insulin therapy (IIT) that demonstrated a reduction in surgical critical care mortality led clinicians to seek to evaluate and improve glycemic control in their practice. Many protocols were developed and implemented in critical care units with varying degrees of effectiveness. The first protocols were paper-based and varied greatly in complexity. Computer support is now being developed to make intravenous (IV) insulin (considered a high-risk drug) safer and easier to use.

The benefits of insulin and glucose control were not surprising to endocrinologists or cardiovascular surgeons. Early reports showed that the use of insulin infusions to improve glucose control was associated with prevention of deep sternal wound infections and lower mortality. Subsequent studies have added evidence to support the use of IIT to reduce morbidity and mortality in critically ill patients, including a subset of medical patients who remain in the intensive care unit (ICU) more than three days. Clinicians still struggle to provide IIT to achieve near-euglycemia without causing hypoglycemia.

There is significant workload associated with frequent glucose monitoring. Point-of-care (POC) testing is a component of nurse-titrated protocols. Current POC methodologies are less precise and more expensive than standard central laboratory methods. Potential errors arise from faulty operator technique, inadequate sample volume and artifacts due to the altered physiology in ICU patients (e.g., hypoxia or low hematocrit). Subcutaneous continuous glucose monitoring technology is only approved for use in outpatients. Research with glucose sensors that may be used in critically ill patients is ongoing.

Although single-center clinical trials have suggested a benefit to lowering glucose to 80-110 mg/dL, a recent multi-center trial was stopped well before the target enrollment because of safety concerns. A large, multi-center trial (NICE-SUGAR) is underway by the Australia-New Zealand Critical Care Clinical Trials group with results expected in 2008. Without more large, prospective trials, questions will remain about the optimal (both safe and effective) glucose endpoint.

With regard to the future it is clear that no matter what research will reveal, clinicians

will no longer ignore blood glucose values as a mere epiphenomenon of critical illness. Glycemic control is essential, although the optimal target remains a topic of discussion. The IIT process will need to be computerized to provide the most consistent ability to follow complex dosing algorithms, and glucose monitoring will need to be far more automated. Closed-loop insulin titration and continuous monitoring would be most desirable.

The CareFusion Center for Safety and Clinical Excellence hosted an international conference that brought together some of the world's leaders in glycemic control research, therapy and monitoring to discuss the latest findings in this area. Summaries of their presentations and the spirited roundtable discussion that concluded the conference are compiled in this monograph.

We hope that our readers will recognize the value of this information and experience with IIT and that future systems can be designed to achieve optimal safety and efficacy. We wish to express our sincere thanks to CareFusion for their commitment to medication safety and their sponsorship of this program.

PROCEEDINGS

A Brief History of Tight Glycemic Control: What We Know in 2007, and How We Got Here

Tony Furnary, MD, Starr-Wood Cardiac Group, Portland, OR

Key points

- *Elevated average three-day postoperative blood glucose (3BG) is a risk factor for morbidity and mortality in hospitalized patients with diabetes.*
- *Continuous insulin infusions that control 3BG to near-euglycemic levels normalize the diabetic patient outcomes to non-diabetic levels.*
- *In cardiac surgery patients target glucose level and duration of intravenous (IV) insulin therapy are both key elements of effective tight glycemic control (TGC). Simply stated, the "3" is just as important as the "BG."*
- *The effectiveness of TGC has been proven in:*
 - *Diabetes cardiac surgery patients in the intensive care unit (ICU),*
 - *Non-ICU diabetes cardiac surgery patients through three postoperative days,*
 - *Medical patients who reside in the ICU longer than three days.*
- *Glucose-insulin-potassium (GIK) therapy is not equivalent to continuous insulin infusions.*
- *Intensive glucose control in the ICU with continuous insulin infusions followed by subcutaneous control on the wards have not produced equivalent results to three days of IV insulin infusions.*

This brief history reviews the major studies of tight glycemic control (TGC) from 1992 to 2007. These five major studies combined have evaluated the effects of TGC on more than 31,000 patients. The studies considered here in chronological order include the Portland Diabetes Project¹⁻⁶ on cardiac surgery patients with diabetes, the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study¹⁻⁷, the Leuven studies by Van den Berghe, et al. in the surgical intensive care unit (SICU)⁸ and medical ICU (MICU)⁹, the Stamford ICU studies by Krinsley^{10,11}, the CREATE-ECLA¹² multicenter study and the multicenter DIGAMI-2 study¹³.

Portland Diabetic Project

Effects of hyperglycemia on cardiac surgery patients. The Portland Diabetic Project was started in 1992 as a prospective, nonrandomized interventional study to evaluate the effects of hyperglycemia and its reduction with continuous intravenous (IV) insulin infusions on morbidity and mortality in cardiac surgery patients. Between 1987 and end of 2005, 5,534 patients had been enrolled in this ongoing study. This number included approximately 4,500 coronary bypass, 470 valve, 570 valve coronary artery bypass graft (CABG) and 60 additional patients who had other cardiac surgical procedures. Pre-admission (out-

patient) glycemic control strategies in this patient population included subcutaneous (SQ) insulin therapy in 31% and only oral hyperglycemic agents in 52%, while 12% were managed with diet control alone, and five percent were undiagnosed and not previously treated at the time of admission for cardiac surgery.

One thousand of the 5,534 patients with diabetes were treated using our first protocol, which was a very intensive SQ insulin protocol, administering SQ doses of regular insulin every four hours. The other 4,500 patients were managed using some version of the "Portland Protocol." In this protocol blood glucose was assessed for every patient every 30 minutes to two hours throughout their hospital stay. In the ICU glucose was measured using blood from an arterial or venous line, and in non-ICU general nursing units, with blood obtained using capillary fingerstick. If an ICU patient's blood glucose was very high or very low, it was monitored every 30 minutes, and in the operating room, every 20 to 30 minutes. For purposes of data analysis the glycemic state of each patient was described by a single number, the average three-day postoperative blood glucose (3BG) i.e., the average of all glucose measurements on the day of surgery and first and second postoperative days, derived from 24 to 72 glucose measurements made per protocol during that period of time.

The Portland Protocol blood glucose target range became progressively lower over time as our goal was to ultimately achieve

euglycemia in all patients. Between 1987 and 1991 treatment was started with SQ insulin with a target blood glucose of < 200 mg/dL. In 1992 we were the first to implement intensive glycemic control using continuous insulin infusions. Our institutional review board (IRB) required proof that intensive glycemic control would not lead to hypoglycemia-related fatalities, so we began the IV insulin phase of the project with a target range of 150-200 mg/dL and limited this therapy to the ICU.

In 1995 after analyzing the initial data we realized that to truly cause change, we had to implement intensive glycemic control not only in the ICU but also in the operating room and in non-critical care patient care areas. The 3BG concept began when we realized that the second major factor in TGC is not where a patient is being treated in the hospital (e.g., in the ICU or in a general nursing unit) rather, it is the length of time (the duration of glycemic control since a patient's acute event) that truly matters. In 1995 we began using continuous insulin infusions on the non-ICU telemetry floor and maintained a target of 150-200 mg/dL. In 1999 we lowered the target range to 125-175 mg/dL; in 2001, to 100-150 mg/dL; in 2004, to 80-120 mg/dL; and in 2005, to 70-110 mg/dL. In 2005 the 3BG, which includes the initial phase of induction through transition to a general nursing unit, for all our patients was 121 mg/dL. We had essentially eliminated hyperglycemia from our patient population.

Early results. We first reported on the relationship between hyperglycemia and cardiac surgery outcomes in a presentation to the annual meeting of the Society of Thoracic Surgeons in 1995⁶. Whether the data were analyzed with a single cutoff of > 175 mg/dL or by 50 mg/dL-increments, our results showed that the postoperative level of blood glucose, as measured by 3BG, has an independent effect on the incidence of deep sternal wound infection. Multivariate analysis showed that the deep sternal wound infec-

tion rate approximately doubles with every 50 mg/dL increase in blood glucose above 175 mg/dL³. These findings were presented in 1995 and published in 1997. It took two years to get these data published, because the findings were so different from the traditional concept of "benign hyperglycemia" that reviewers were reluctant to believe the results.

Investigating further, we evaluated the effect of the individual (daily) components of 3BG on infection rates. We found that with three days of TGC, preoperative hemoglobin A1c has no bearing on infection. However, preoperative blood glucose > 180 mg/dL does have a significant effect. Blood glucose on the day of surgery has no bearing on infection, but blood glucose > 180 mg/dL on the first, second and third postoperative days all have an independent effect on infection rates¹⁴.

We also found a highly significant difference between patients whose glucose levels were inadequately controlled or only partially controlled with SQ insulin compared to those who were managed using continuous insulin infusions. In the later group, the infection rate decreased to 0.7% as compared to a rate of 2% in the SQ group ($p < 0.001$)¹. Interestingly, at that time, in the mid 1990s, the diabetic cardiac surgery patient population worldwide had an overall incidence of deep sternal infection of 5.6%. So our infection rate of 2%, even in the subcutaneously treated population was very low compared to that reported in the world literature at the time. This demonstrated the significant effects of targeted glycemic control even with SQ insulin therapy when compared to the previous standard of care¹⁴.

The results obtained with continuous IV insulin therapy were better still. Multivariate analysis showed that continuous insulin infusions independently reduced the risk of infection by 63%. The independent effect of IV

insulin on deep sternal infection rates was published in 1999¹. Not since the discovery and subsequent clinical introduction of penicillin in the 1930s and early '40s, respectively, has there been a non-surgical intervention that has so dramatically altered surgical-site infection rates.

Based on these studies we concluded that diabetes itself was not a risk factor for infection. Rather it was the presence of hyperglycemia in the diabetes population that is the true risk factor for infection. Furthermore, this risk can be reduced by 63% through the use of three postoperative days of TGC with continuous insulin infusions.

Acute mortality. In 1999 we presented data at the American Heart Association that compared 3BG levels to mortality in the coronary bypass (CABG) population². For CABG patients, when the 3BG was > 200 mg/dL, the mortality was 6% and when the 3BG was < 200 mg/dL, the mortality was only 1.5%. Multivariate analysis showed that 3BG is a highly significant independently predictive variable for mortality. The mortality rate increases by two-fold for every 50 mg/dL increase in 3BG.

At a time when it was commonly thought that there was nothing wrong with hyperglycemia in the postoperative patient, we established hyperglycemia as an independent risk factor for mortality in CABG patients. Again, independent analysis of the various components of 3BG showed that hemoglobin A1c is not predictive of mortality, nor is preoperative glucose, but elevated glucose is a significant independent risk for death. Blood glucose levels on the first and second postoperative days, and, for patients who remain in the ICU, the third day are also significant predictors of in-hospital death.

Thus, the duration of hyperglycemia and, conversely the duration of tight glucose management is an important determinant of outcomes related to hyperglycemia in cardiac

surgery patients. Thus, the second critical factor in TGC management (the first being target blood glucose level) is not location of the patient (ICU or the operating room or non-ICU floor); rather, it is the duration of TGC therapy. It is the critical three-day period immediately following the seminal ICU admission event during which hyperglycemia significantly affects outcomes. For patients who remain in critical condition, it continues to affect outcomes for as long as the patient remains in the ICU.

SQ vs. continuous insulin infusion. We have shown that continuous insulin infusions reduce absolute unadjusted mortality rates by more than 50% in CABG patients who also have diabetes. Multivariate analysis shows that the risk-adjusted independent effect of continuous insulin infusions is to reduce mortality by 65%.

Our annualized mortality rates show that after continuous insulin infusions were used in the patients with diabetes, by 1995 the risk of death was normalized to that of patients without diabetes. As the average protocol target and actual glucose levels were lowered, results continued to improve. Between 2000 and 2006 the overall mortality for patients with diabetes in our hospital was 0.9%, compared to the national reported Society of Thoracic Surgeons mortality rate of 3.4% in CABG patients with diabetes^{15,16}.

Complications. Publication of our results showed that increasing 3BG is associated with an increasing number of complications, including death, transfusion, new-onset atrial fibrillation and deep sternal wound infection. Low-cardiac-output syndrome and length of stay also increase over time. We did not see a relationship between 3BG and pneumonia, stroke, and other complications¹⁷.

Non-diabetes patients. In 2007 we began looking at the non-diabetes CABG patient population. Although we have applied our Portland Protocols to our non-diabetes patients with stress hyperglycemia since 1998, we have not seen any reduction in mortality in this population of patients. We are now hoping to randomize our non-diabetes patient population with stress hyperglycemia to TGC and non-TGC groups. However, based on our preliminary data, TGC may not make a difference in the non-diabetes cardiac surgery population.

DIGAMI-1

Diabetes and acute myocardial infarction (AMI). While we were publishing our findings from 1995 through 1998, others were working on this problem, including the effect of the management of diabetes on AMI mortality. Most studies had shown that in every era of cardiac intervention – from the 1960s through the present – patients with diabetes had a two-fold higher mortality for AMI compared to those without diabetes¹⁸.

When thrombolysis became part of cardiac care between the mid-1980s and 2000, overall mortality decreased, yet diabetes still had a higher mortality for AMI. Since 2000, patients with diabetes who have an AMI still have a two-times-higher incidence of mortality than the total patient population. Therefore, diabetes seems to be a risk factor for death following AMI.

Even in patients without diabetes there is a relationship between severe hyperglycemia and mortality. Pooled meta-analysis data show that the pooled risk factor is about 2.8 to 5.8 or about a four-fold increase in risk. Hyperglycemia is also a risk factor for myocardial infarction.

The DIGAMI-1 study⁷ reported by Klas Malmberg in 1995 evaluated patients who had an AMI and blood glucose concentrations greater than 200 mg/dL. Intensive insu-

lin treatment used in the ICU included IV insulin for more than 24 hours, then four SQ injections a day for the next three months. Mortality was reduced by 20% during the three to four years patients were evaluated. In-hospital mortality was not reduced but long-term survival improved. Lower glucose upon admission was associated with lower in-hospital mortality. Although this association was not significant, there was a trend towards a lower mortality in the group with lower glucose.

The patients in the insulin-treated group also had better long-term survival. These patients were tightly controlled, versus the control group that was not tightly controlled. For patients who were initially not on insulin therapy at the time of admission for AMI and who were then placed on insulin and very tightly controlled, the survival advantage was even greater over the next few years. Those findings were published in 1997.

DIGAMI-2

Glucose, insulin and potassium (GIK). The randomized DIGAMI-2 study by Malmberg, Lars Ryden, et al. in 2005¹³ included 48 hospitals in six countries and 1,200 patients who were assigned to three treatment arms. Group One received a solution of GIK for 24 hours followed by home insulin therapy. Group Two was given GIK infusion followed by standard glucose control. Group Three had routine metabolic management. No statistical differences were found between these three groups in terms of outcomes. There were no differences among the major etiologic factor, glucose and the major primary outcome, mortality. Glucose control in all three groups was exactly the same over time and therefore did not produce a separation of the outcomes curve. However, a multivariate analysis of mortality in the DIGAMI-2 shows three very significant risk factors for long-term death. Increased age, serum creatinine, heart failure and higher

fasting blood glucose concentrations all negatively affected survival.

In the CREATE-ECLA trial¹² cardiologists at 470 centers around the world evaluated patients with elevated-S-T myocardial infarction. The goal was to evaluate whether use of the GIK protocol reduced 30-day mortality and other measures in AMI patients. Results showed no difference in the primary endpoint of mortality. The blood glucose levels in the control (non-GIK) group were lower than the blood glucose levels in the GIK group, so that any advantage that insulin might have conferred was taken away by the disadvantage of increased glucose levels. The study showed no reduction in mortality because the study design did not create a separation in the primary variable hypothesized to affect mortality, i.e., blood glucose levels.

However, if these data are divided into glucose terciles, mortality increased with increasing glucose levels. Patients in the lowest third of glucose levels had the lowest mortality rate. In the middle third mortality was higher, and in the highest third there was significantly higher mortality. Even though this study is considered a negative study, it shows a relationship between hyperglycemia and mortality.

From these studies on AMI one can conclude that GIK is not effective in altering outcomes. Over the past 40 years multiple studies utilizing GIK have been carried out to investigate its efficacy in reducing mortality. Not one of these studies has produced a significant positive result. Outcome improvement has only been associated with the use of insulin therapy to achieve glucose control.

The Leuven studies / Van den Berghe

Intensive insulin therapy (IIT) in cardiac surgery patients—prospective, randomized trial. In 2001 Van den Berghe⁸ published a landmark trial of 1,500 patients that showed

results similar to the early results from the Portland Diabetic Project. In this prospective, randomized study patients were assigned to an IIT (target glucose < 110 mg/dL) or a non-IIT group (180-200 mg/dL). It is important to note that 60% of enrollees were postoperative cardiac surgery patients. IIT was associated with a 34% reduction in mortality, a 46% reduction in infection, a 41% reduction in dialysis, a 50% reduction in transfusions and a marked reduction in peripheral nerve polyneuropathy.

The majority of the reduction in mortality occurred in patients who were in the ICU and kept on insulin infusion for five days or longer. In the study hospital, insulin infusions are not used in general nursing care areas. If patients were transferred out of the ICU after the first or second day, they only had one or two days of TGC and then the glucose concentrations increased. A reduction in mortality was not seen in this subset of patients. Therefore, in Van den Berghe's first surgical study, there is confirmation of the duration component of continuous insulin infusions or ITT therapy previously described by the Portland series. A follow-up study from Leuven showed that the survival benefit achieved in the hospital is maintained up to three or four years after surgery.

Medical ICU. In 2006 in a population of 1,200 MICU patients, Van den Berghe examined in-hospital mortality between groups randomized to TGC (80–110 mg/dL) or less intensive glycemic control (< 180 mg/dL). They found a significant effect of ITT on mortality for patients who remained in the ICU three days or longer. For those who were in the MICU for less than three days there was no apparent effect of ITT on mortality. In patients in the ICU for three days or longer, the mortality risk reduction was about 18%, which was highly significant.

Stamford / Krinsley

Hyperglycemia in medical/surgical ICU patients—retrospective data review. A corroborating study by James Krinsley was based on a retrospective data review of 1,800 patients at Stamford Hospital between 1999 and 2003¹⁰. The study showed a direct relationship between increased mean ICU glucose levels and increased mortality in a mixed, medical/surgical ICU that did not include cardiac surgery patients. In Van den Berghe's study, 65% were cardiac surgery patients, and the cardiac surgery population itself likely had a significant effect on the results seen. In Krinsley's non-cardiac surgery ICU population, patients observed with blood glucose levels of 150 mg/dL had a three-fold increase in mortality compared to the group with the lowest blood glucose values of 90 mg/dL. Krinsley concluded that increased glucose levels adversely affect mortality rate even in non-cardiac surgery populations.

Length of stay. In 2006 Krinsley reported¹⁹ that hyperglycemia was also related to increased length of stay. Insulin infusions, which reduce hyperglycemia, were shown to decrease hospital costs. From the Portland data, IIT on the day of surgery and the first and second postoperative days has been shown to reduce length of stay. Overall, insulin infusions reduce the length of stay by about two days in cardiac surgery patients.

What Do We Know About TCG at the End of 2007?

From the Portland study we know that:

- Mortality is affected by glucose on the day of surgery, the first day and the second day post-surgery, but the effect becomes insignificant on the third day.
- Infection rates are affected preoperatively, are almost significant on the day of surgery ($p = 0.7$) and are significant on the first, second, and third day postoperatively.

- Length of stay is affected on the first, second and third day, and even preoperatively.
- In cardiac surgery patients the “3” is just as important as the “BG.” Both express the important terms of this therapy–target level and duration.

In general, this is what we know about TGC in the cardiac surgery population is this (Table):

- In CABG patients with diabetes who have hyperglycemia and insulin infusions, TGC has been shown to be significant on admission, in the operating room, on the day of surgery, in the ICU and in the ward. Beyond the third postoperative day, the relationship is not significant.
- In CABG patients without diabetes, no significant association has been shown between hyperglycemia and mortality, infection or length of stay.
- In the diabetes non-cardiac surgery , non-CABG cardiac surgery patients, i.e., isolated valves, aorta, the only factor associated with glucose control is infection. This association occurs in the ICU and on the ward out to the third day. Beyond the third postoperative day there is no association. Glucose control in the operating room on the day of surgery has no significant effect on infection rates.
- There have been no publications about the impact of glucose control in non-CABG patients who do not have diabetes.

Although TGC is being widely advocated, it has only been shown to be of significant value in about 30% of patient populations. In non-cardiac surgery patients the supporting evidence is even less. TGC has been shown to have significant impact on mortality, infection and length of stay for surgical patients while they are in the ICU.

Table. TGC Proven Effectiveness and Hyperglycemia a Proven Risk Factor as of December 2007

Hospital Location:	Admission	OR/DOS	ICU	Ward-POD#3	> POD #3
Patient Population:					
DM-CABG	I (A)	ML (A)	MIL (A)	I (A)	NS (A)
Non-DM CABG	NS	NS (B)	NS (B)	NS (B)	NS (B)
DM- non-CABG	I (A)	NS (B)	I (A)	I (A)	NS (B)
NonDM,non-CABG	Unk	Unk	Unk	Unk	Unk
Non-CTS Surgical	Unk	NS (A)	MIL (A)	Unk	Unk
Medical	Unk	NA	M (A)	Unk	Unk
AMI Cardiac	NS (A)	NS (A)	NS (A)	Unk	S (A)
Neurologic (CVA)	Unk	NA	+ (A)	Unk	Unk

Significant for: M= Mortality, I = Infection, L = LOS; S = Long term Survival; NS = Non-significant; Unk = unknown; NA = Not Applicable; **Levels of evidence:** A = proven by multiple randomized trials; B = suggested by one or two observational studies; C = based on consensus opinion, not proven in clinical trials

For medical ICU patients, Van den Berghe has shown that if a patient received TGC for more than three days, it improves mortality rates. There are no published data in the non-cardiac surgery populations about the impact of TGC in the operating room and in general nursing units.

In the cardiac myocardial infarction population, TGC has not shown a significant impact on admission to or length of stay in the ICU. We have not demonstrated changes in outcomes despite an association between glucose concentrations and TGC. In surgical patients, beyond the third postoperative day there is a significant association with survival rates based in the results of the DIGAMI-1 Study.

In patients with strokes in the ICU, insulin infusions decrease the extent of the stroke.

Conclusions

- The effectiveness of TGC is proven in:
 - Diabetes cardiac surgery patients in the ICU,
 - Non-ICU diabetes cardiac surgery patients through three days,

- Medical ICU patients who are in the ICU longer than three days.

- Benefit is probable in surgical patients in the SICU longer than three days. Benefit is considered as “probable” because non-cardiac surgery patients were never separated out from the cardiac surgery patients in the Van den Berghe study.
- Benefit is also possible in patients with diabetes who have a myocardial infarction and have percutaneous coronary intervention. This possible benefit is only inferred from adverse data related to hyperglycemia, for the beneficial effects of insulin have never been proven in this patient population.
- Benefit has not been proven, or is unlikely in
 - Cardiac surgery patients without diabetes,
 - Medical ICU patients in the ICU for less than three days,
 - AMI patients without diabetes.

We can conclude that:

- 3BG is a true risk factor for morbidity and mortality in CABG patients with diabetes

- Continuous insulin infusions that control 3BG can normalize the diabetic patient outcomes to non-diabetic levels.
- GIK is not equivalent to continuous insulin infusions.
- TCG in the ICU with continuous infusions followed by SQ control in general nursing units has not produced equivalent results to three days of IV insulin infusions.

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PROCEEDINGS

Intensive Insulin Therapy and the NICE-SUGAR Study

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Key points

- The landmark studies by Van den Berghe et al. have made control of blood glucose a central part of the management of critically ill patients, but other randomized, controlled trials have been unable to replicate their results.
- As a result of the two conflicting Van den Berghe trials and concerns over case mix, higher-than-expected mortality in the control group, and routine use of high-dose intravenous glucose, intensive-care clinicians remain uncertain whether to use intensive insulin therapy (IIT) in their patients.
- The largest trial of IIT will be the NICE-SUGAR study, which compares the effects of the two blood glucose targets—4.5–6.0 mmol/L (80–110 mg/dL^a) and 8.0–10.0 mmol/L (180–200 mg/dL)—on 90-day, all-cause mortality in intensive care patients who are predicted to be in the intensive care unit on more than two calendar days.
- If the NICE-SUGAR study demonstrates a favorable treatment effect, maintaining normoglycemia will most likely become a treatment standard worldwide.

Published observational data show a decrease in unwanted outcomes accompanying improved glycemic control in cardiothoracic surgery patients and in those admitted to a mixed population intensive care unit (ICU)¹⁻³. While it is tempting to conclude that these data are evidence of “cause and effect,” other reports suggest that it is hazardous to make such inferences. Two examples illustrate this point:

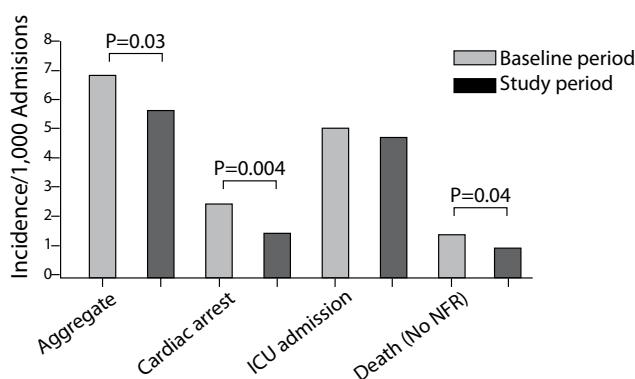
The MERIT study was a cluster, randomized, controlled trial (RCT) that studied the impact of introducing medical emergency teams (METs) on unanticipated ICU admissions, and on cardiac arrest and death in patients without a DNR order in Australian hospitals⁴. In this study, a significant reduction in the incidence of cardiac arrests and

deaths (Figure 1) was observed. It would be natural to attribute this reduction to the introduction of the METs, but as the reduc-

tion was observed in the control hospitals it illustrates the danger of attributing clinical changes to specific interventions.

A second study evaluated the mortality rates in patients presenting with severe sepsis to emergency departments of Australian and New Zealand hospitals. These data were obtained while planning a phase III trial to validate Rivers’ study of early goal-directed therapy⁵. There was a steady decrease in the case fatality rate with crude hospital mortality decreasing from 37.7% in 1998 to 21.2% in 2005⁶. There were no specific interventions to which this decrease could be attributed, illustrating that dramatic reductions in mortality may occur over time both with and without changes in management. For common conditions, such as hyperglycemia in critical illness, decisions about appropriate choice of therapy should be made on the basis of RCTs. Observational data are useful for confirming

Figure 1.



Incidence of aggregate outcome, cardiac arrest, death and unanticipated ICU admissions during baseline and study periods in control hospitals in the MERIT study. (From data in [4]).

the findings of RCTs and for investigating rare but serious side effects, but are subject to large errors due to bias^{7,8}.

Intensive Insulin Therapy (IIT) Studies—Van den Berghe et al.

In their first randomized trial, Van den Berghe et al. randomized 1,548 surgical intensive care patients to receive insulin to maintain blood glucose between 4.4-6.1 mmol/L (80-110 mg/dL^a) (intensive insulin group) or between 10-11.1 mmol/L (180-200 mg/dL) (conventional insulin group)⁹. The study reported an absolute reduction in hospital mortality of 3.7% (relative risk reduction, RRR 33%) with IIT⁹. Other benefits reported in the intensive insulin group were a reduction in hospital stay, blood stream infections, acute renal failure requiring dialysis, incidence of critical-illness polyneuropathy and blood transfusions. The external validity of the results has been questioned because study patients received high doses of intravenous (IV) glucose and the control group mortality was unexpectedly high. Many consider the RRR to be implausible¹⁰. There was no difference in the number of deaths occurring during the first five days in intensive care, and the reduction in mortality was limited to patients receiving more than five days' treatment in the ICU. The incidence of hypoglycemia was significantly increased in the intensive insulin group (39 patients) compared to those in the conventional glucose group (6 patients). No long-term sequelae from hypoglycemia were detected.

In February 2006, Van den Berghe et al. published a second RCT in 1200 critically ill medical patients expected to be treated in the ICU for three or more days¹¹. The study did not find a significant reduction in mortality in the intention-to-treat population, although in an a priori subgroup of 767 patients who were in the ICU on three or more calendar days, 90-day mortality was reduced from 49.1% to 42.2% (RRR 14.1%, $p=0.06$). The investigators

were not able to predict accurately how long each patient was likely to stay in the ICU. The publication of this second study has increased clinicians' uncertainty over the role of IIT in critically ill patients. Van den Berghe called for additional large-scale RCTs of at least 5,000 participants to answer the important question of whether IIT reduces mortality in ICU patients. Van den Berghe's call was supported by an accompanying editorial highlighting the need for further study to answer this important question¹².

The NICE-SUGAR Study

As a result of the two conflicting Van den Berghe trials and concerns over case mix, higher-than-expected mortality in the control group and routine use of high-dose IV glucose, ICU clinicians are still uncertain about using IIT in their patients. To resolve this uncertainty, a National Health and Medical Research Council (NHMRC)-funded RCT of IIT commenced in Australia and New Zealand in 2005, and in 2006 the Normoglycaemia in Intensive Care Evaluation (NICE) Study Investigators joined with the Survival Using Glucose Algorithm Regulation (SUGAR) trial investigators of the Canadian Critical Care Trials Group to complete a single trial thereafter called the NICE-SUGAR study¹³.

The primary aim of the NICE-SUGAR study is to compare the effects of the two blood glucose targets on 90-day, all-cause mortality in intensive care patients who are predicted to be in the ICU on more than two calendar days. The null hypothesis is that there is no difference in the relative risk of death between patients assigned a blood glucose target of 4.5-6.0 mmol/L (81-108 mg/dL) and those assigned a blood glucose target of less than 10.0 mmol/L (<180 mg/dL) with insulin being infused if blood glucose exceeds 10.0 mmol/L (180 mg/dL) and adjusted when needed to maintain blood glucose of 8.0-10.0 mmol/L (144-180 mg/dL).

The two blood glucose targets are achieved with the aid of a web-based algorithm. The use of this algorithm promotes uniform blood glucose management in all study sites and enables the study management committee to monitor blood glucose management within the study. It is therefore known whether the blood glucose targets are being met with sufficient separation between the two groups. After more than 1.5 million hours of blood glucose management, the average blood glucose derived from measurements entered into the treatment algorithm is 5.9 mmol/L (106.2 mg/dL) in the lower range group versus 8.4 mmol/L (151.2 mg/dL) in the higher range group. This compares with 5.7 vs. 8.5 mmol/L (102.6 vs. 153.0 mg/dL) in the first Van den Berghe study and 6.2 vs. 8.5 mmol/L (111.6 vs. 153.0 mg/dL) in the second study. The average time on study treatment is 386 hours or 16.1 days.

The major safety concern with IIT is hypoglycemia. The rate of hypoglycemia for patients randomized to the low-range arms of the two Van den Berghe trials was 5% and 18% respectively^{9,11}. In 4,450 patients the rate of hypoglycemia in the low-range group of the NICE-SUGAR study is 10.2 events per 100 patients, towards the lower end of the rates reported for this treatment. All episodes of hypoglycemia are classified as serious adverse events (SAEs) and reported to participating centers' ethics committees and to the study's independent data and safety monitoring committee. All SAEs have been followed up by the study management committee and to date there have been no harmful sequelae detected.

The data from the two Van den Berghe studies suggest that in a combined medical and surgical population a RRR of 14% is a more appropriate target, and 6,100 patients will be included in NICE-SUGAR to provide 90% power to detect a 14% RRR from a baseline mortality of 30% ($\alpha < 0.05$).

NICE-SUGAR Research Plan^b

Patient Selection

The treatment effect in the first Van den Berghe study was limited to patients who were in the ICU for five or more days. In the second study only patients expected to be in the ICU for three days were included. In the NICE-SUGAR study patients expected to be discharged alive or die before the end of the day following admission are not being included. To exclude patients who will stay in the ICU for more than two calendar days but who have a very low risk of death, patients who are able to eat (or who are tube-fed due to pre-existing bulbar or laryngeal dysfunction) and patients who do not have an arterial line as part of their routine management are also being excluded. Patients who are moribund and at imminent risk of death (brain death or cardiac standstill) are excluded on the basis that treatment allocation cannot alter their outcome. Randomization is achieved via a password-protected, encrypted, secure study website with patients allocated to receive one of two target ranges for glycemic control in the ICU. A minimization program stratifies treatment allocation by type of critical illness (medical vs. surgical) and by region: Australia and New Zealand or North America.

Study Outcomes

Primary outcome measure:

- All-cause, 90-day mortality

Secondary outcomes:

- Death in the ICU, by day 28 and before hospital discharge
- Length of ICU stay
- Length of hospital stay
- The need for organ support (inotropes, renal replacement therapy and positive pressure ventilation)
- Incidence of bloodstream infections
- Incidence and severity of hypoglycemia

- In the subgroup of patients admitted with diagnosis of traumatic brain injury, long-term functional status will be determined by Extended Glasgow Outcome Scores (GOSE) at six months and two years.

Organization and Collaboration

The study is being conducted as a collaboration among the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), the Canadian Critical Care Trials Group (CCCTG) and The George Institute for International Health and overseen by the NICE-SUGAR study management committee. Data analysis, data sharing, and publication regulations will involve all investigators according to ANZICS CTG guidelines and will be regulated by memoranda of understanding.

The group assembled for this study includes epidemiologists and intensive care physicians who provide the expertise and clinical and research skills to conduct this study. The collaboration between the Australian and New Zealand and Canadian Critical Care Trials Groups and the Mayo Clinic will provide reliable evidence about the comparative effects of different targets for blood glucose concentration in patients treated in the Australasian and North American intensive care setting.

Summary

The two studies conducted by Van den Berghe et al have made control of blood glucose an important issue in the management of critically ill patients. To date, other RCTs have been unable to replicate the results of these studies. The NICE-SUGAR Study will be the largest trial of IIT, and if it demonstrates a favorable treatment effect, maintaining normoglycemia will most likely become a treatment standard worldwide.

- a. $\text{mmol/L} = (\text{mg/dL} \times 10) \text{ divided by atomic weight of glucose (MW} = 180), \text{ i.e., } \text{mmol/L} \times 18 = \text{mg/dL of glucose}$

- b. See electronic supplement to Angus and Abraham, 2005¹³

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European Multi-center Trials with Tight Glucose Control by Intensive Insulin Therapy

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Key points

- *In contrast to the decreases in mortality and low severity of adverse effects reported when insulin infusion rate was titrated to keep blood glucose levels between 80-110 mg/dL, these benefits were not confirmed in multi-center prospective studies.*
- *Retrospective data analysis found an association between a mean blood glucose level below 140-150 mg/dL and improved outcome.*
- *Currently unresolved issues in intensive insulin therapy (IIT) include the optimal blood glucose target, the effects of high variability in blood glucose levels, the risks and hazards of hypoglycemia and the potential influence of an underlying disorder on the effects of tight glucose control (TGC).*
- *Although recommendations regarding the practical aspects of TGC IIT cannot presently be made, an intermediate target level for blood glucose seems to be associated with the lowest risk-to-benefit ratio.*

Tight glucose control (TGC) by intensive insulin therapy (IIT) is defined as the maintenance of “normoglycemia” (blood glucose levels 80-110 mg/dL). Achieving TGC by the titration of intravenous (IV) insulin has become a major topic of interest. The common condition of “stress hyperglycemia” as a physiological response to a critical illness was challenged by the report of Greet Van den Berghe and co-workers in Leuven. They reported a 4% decrease in absolute mortality associated with TGC IIT in a surgical intensive care unit (ICU) population¹. The beneficial effects of TGC IIT were partially confirmed by the same team in a medical ICU population².

New insights into the mechanisms of glucose toxicity have also been described. Severe hyperglycemia was found to induce acute changes in cellular metabolism and

in the structure of macromolecules^{3,4}. In the presence of high glucose concentrations, several steps in the glycolytic pathways can induce the release of toxic derivatives. These effects, sometimes collectively referred to as “the Brownlee theory,” are reversible with the pharmacological inhibition of Poly-ADP-ribose polymerase⁵, suggesting the involvement of the activation of this enzymatic complex of nuclear repair enzymes. This is probably related to the involvement of reactive oxygen intermediates in the toxic effects of hyperglycemia^{6,7}.

These clinical and biochemical findings support the concept of hyperglycemia as a mediator for rather than a marker of critical illness. Proof that hyperglycemia is an independent risk factor for ICU mortality in critically ill patients is lacking⁸. Several dif-

ferent teams tried to confirm the results of the Leuven team in prospective, randomized trials, including the German VISEP trial, the Australian NICE-SUGAR trial and the European Gluconcontrol study, while others analyzed retrospectively collected data^{9,10,11,12}.

Multi-center Trials of TGC IIT

VISEP. The German Competence Network Sepsis (SepNet), a publicly funded, independent, collaborative study group, designed the randomized VISEP trial¹³ to address two questions in a group of septic patients (colloids versus crystalloids and TGC IIT). This trial was stopped for safety reasons after 488 patients in 17 centers were enrolled between April 2003 and March 2005. Of these, 247 received intensive insulin therapy (IIT [goal: 80-110 mg/dL]) and 241 received conventional insulin therapy (CIT, [goal: 180-200 mg/dL]). Interim data analysis showed that 30 patients (12.1%) treated with IIT developed hypoglycemia, compared to 5 patients (2.1%) treated with CIT ($p < 0.001$). No adverse event was classified as leading to patient death. No differences were found in the 28-day (21.9% vs 21.6%; $p = 1.0$) and 90-day mortality rates (32.8% vs 29.5%; $p = 0.43$) for IIT and CIT, respectively. Since the observed rate of hypoglycemia was considered unacceptably high and since there was no treatment efficacy (no significant difference in 28- or 90-day mortality), the Independent Data Monitoring Committee (IDMC) strongly recommended that the insulin arm of the trial be stopped.

Glucontrol. This prospective, randomized, controlled, multi-center study¹⁴ compared the effects of TGC IIT to a control group with less abnormal blood glucose concentrations than in patients in the Leuven studies (140-180 mg/dL). The primary outcome measure was ICU mortality. Twenty-one ICUs participated on a voluntary basis (i.e., no financial incentive or defrayment of study-related costs). This study was stopped for safety reasons by the Data Safety Monitoring Board (DSMB) after the first interim analysis because of a high rate of unintended protocol violations. A total of 1,011 patients (550 in the IIT arm, 551 in the CIT arm) were enrolled. Patient characteristics (median age 65 years, medical patients 41%, males 62.7%, APACHE II score at admission 16.5 ± 7.0) did not differ between groups. From the time of admission the mean blood glucose levels calculated from individual blood glucose values were higher in the CIT than in the IIT group with a median value of 119 (IQR 110-131) mg/dL in the IIT group and 147 (IQR 128-165) mg/dL in the CIT group, $p < 0.0001$. The adherence to the experimental protocol was confirmed by the proportion of time spent in the assigned range (40.8% and 38.2% for the IIT and CIT groups, respectively). The ICU mortality was slightly higher in the IIT compared to the CIT group (16.7% versus 15.2%, NS). Multivariate analysis showed a significant association between APACHE II and SOFA scores on admission and higher mortality. The rate of hypoglycemia was higher in the IIT (9.8 %) than in the CIT group (2.7%, $p < 0.0001$). Assignment to the IIT group, death in the ICU, and APACHE II scores were significantly associated with hypoglycemia.

Multi-center Trial Results. The currently available results of both multi-center trials do not seem to confirm the Leuven data and actually raise additional clinically important concerns, questions and difficulties that must be resolved before widespread use of TGC IIT

for critically ill patients in ICUs worldwide can be recommended.

Optimal Target for Blood Glucose

The answer to the question of optimal blood glucose target level can probably be inferred from clinical data rather than from experimental findings. Indeed, in the various studies the detrimental effects of hyperglycemia were observed in the presence of blood glucose levels higher than those observed in patients and therefore could be irrelevant for the determination of the optimal glycemia. Based on the data from the two Leuven studies^{1,2}, blood glucose > 200 mg/dL can probably no longer be considered an acceptable target for insulin therapy in critically ill patients. However, the issue of the safest range below this level is still unresolved and has not been specifically addressed in prospective clinical trials to date.

Three large retrospective trials^{9,10,11} found that blood glucose levels < 140 mg/dL were associated with an improved outcome compared with higher levels.

Ideally, the optimal target for blood glucose levels should be defined by large prospective trials comparing two ranges¹⁵. The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) and the Glucontrol study were designed and launched to compare the effects of insulin therapy titrated to target blood glucose levels of 80-110 mg/dL versus 140-180 mg/dL. The results of the Glucontrol study to date suggest that a blood glucose target of 140-180 mg/dL is safer than 80-110 mg/dL. Even though further confirmation of these findings is desirable, most clinicians presently use this intermediate range of 140-180 mg/dL as a target for IIT^{16,17}.

Detrimental Effects of High-glucose Variability

Egi and colleagues¹⁸ performed a multivariate logistic regression analysis of retrospectively collected data from 7,049 critically ill patients. The coefficient of variability calculated from the standard deviation of blood glucose values recorded for each patient appeared to be closely related with survival. In patients with diabetes, blood glucose variability was a stronger predictor of ICU mortality than was the absolute blood glucose value. Outside the ICU, recent data recorded in diabetic patients and compared to volunteers also indicate that blood glucose fluctuations increase the oxidative stress¹⁹. These clinical data may reflect "cellular" data that showed cell damage to be most prominent when blood glucose changed rapidly from a normal to an elevated level (reviewed in Brownlee³).

This potentially important issue of glucose variability was not analyzed in the large trials performed in critically ill patients published to date. In the Glucontrol study¹⁴, the blood glucose standard deviation was identical in the two treatment arms.

One implication of the discovery of the importance of keeping blood glucose as stable as possible could be to favour the use of strict algorithms to maintain blood glucose within a narrow range. Although several different validated algorithms are available, indices of blood glucose variability usually were not assessed and not used to compare different protocols.

Risks and Hazards of Hypoglycemia

Hypoglycemia is the major fear when starting IIT and justified the interruption of the two European multi-centre prospective trials mentioned above. Even if the incidence of hypoglycemia was substantial in both Leuven studies^{1,2}, the condition of the patients experiencing hypoglycemia was not worsened. Of note, blood glucose monitoring was very

tight, which implies that the duration of the hypoglycemic episodes was definitely short. Therefore, the possibility that long-lasting hypoglycemia may be deleterious or even life-threatening cannot be ruled out. Using IIT titrated to maintain normoglycemia requires careful blood glucose monitoring, since the classical neurological symptoms can be offset by sedation or by an underlying impairment of the mental status.

Some categories of patients with significant dysfunctions of neoglucogenic organs (liver and kidney), with adrenal failure leading to an impaired responsiveness of counter-regulatory hormones, or with a delayed elimination of insulin could experience longer episodes of hypoglycemia. The effects of TGC IIT in these subgroups need to be carefully assessed.

Potential Influence of the Underlying Disorder on the Effects of TGC IIT

In the second Leuven study², the improvement in mortality was seen only in patients who were in the ICU three days or longer. Mortality tended to increase in patients with a shorter length of stay who were randomized to the IIT group. Some secondary outcome variables (see Devos and Preiser²⁰ for discussion) such as requirement for dialysis, incidence of bacteremia, requirement for prolonged antibiotic therapy, incidence of hyperbilirubinemia and "hyperinflammation" were not improved in the IIT group. These differences could point out subgroups of patients that do not benefit from IIT. Another category of patients that may not benefit from IIT is the subset of patients with pre-existing diabetes, as shown by the aggregation of the results of both Leuven studies²¹.

At the present stage, there is no definite answer to the question of which subgroups are likely to benefit more from IIT. Patients with myocardial ischemia and after cardiac surgery may represent a subset of patients

susceptible to the deleterious effects of hyperglycemia (reviewed in Devos et al.²²).

Interventional studies performed in specific subgroups or, at least, subgroup analyses of the large multi-center trials are needed to define the categories of patients that will selectively benefit from IIT. Meanwhile, the use of an intermediate blood glucose target is probably more prudent and is presently recommended^{23,24,25,26}.

Conclusions

In spite of the findings that mortality can be decreased in critically ill patients by TGC and restoring normal blood glucose values using IIT, several important questions are still unanswered. These include the issues of the best target range, the importance of minimizing blood glucose variability, the avoidance of hypoglycemia and the delineation of the categories of patients in whom the restoration of "normal" blood glucose is most beneficial. With the notable exception of the VISEP trial, the titration of insulin in order to maintain blood glucose < 180 mg/dL is supported by the currently available clinical data, and an improvement in outcome was consistently associated with blood glucose < 140-150 mg/dL.

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7th Invited Conference–European Multi-center Trials with Tight Glucose Control by Intensive Insulin Therapy

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Implementation of Tight Glycemic Control at Stamford Hospital

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Key points

- *Elements of a successful implementation of a tight glycemic control (TGC) protocol include multidisciplinary collaboration; prior staff experience with complex protocols; an agreed-upon, achievable blood glucose target; robust data-analysis capabilities; and clinician access to relevant intensive care unit (ICU) outcome data.*
- *Avoidance of deleterious severe hypoglycemia requires recognition of the risk factors such as severity of illness, the presence of renal failure (delayed clearance of insulin), sepsis and liver failure (impaired gluconeogenesis), discontinuation of source of calories with continuation of insulin therapy, and diabetes.*
- *TGC has emerged as a standard of care in the ICU because of its biologic plausibility and the available interventional studies. Further corroboration may come from the ongoing NICE-SUGAR trial.*
- *The appropriate treatment threshold—110, 120, 140 or even 150 mg/dL—is not known with certainty and may vary based on diagnostic category. Available evidence, however, does not support maintenance of higher levels of sustained hyperglycemia.*

Before the project discussed in this article, glycemic management in the Stamford Hospital intensive care unit (ICU)—a 14-bed unit where medical, surgical and cardiac patients were treated—was similar to that in most ICUs. Moderate degrees of hyperglycemia were tolerated without consideration for treatment, because this condition was common and believed to be adaptive. After the publication of Van den Berghe's randomized study of intensive insulin therapy (IIT), a program for tight glycemic control (TGC) was implemented at our hospital.

The process of making this change began with a review of a database that includes detailed clinical and financial data for 8,600 consecutively admitted patients to investi-

gate the relationship between glycemic levels and mortality. The results were striking. A nearly linear relationship was found between these two variables even within the range of euglycemia. Further elaboration of these data was published in 2003².

This evaluation identified the importance of glycemic control and prompted discussions with the ICU nurses about the type of treatment protocol that should be instituted in the unit. It became clear that the nurses were unwilling to implement a protocol with a blood glucose target of 80-110 mg/dL. The nurses feared the work burden imposed by strict monitoring and treatment and the risk of hypoglycemia, particularly if such a strict target was established. After discussion, it

was agreed that 140 mg/dL would be an acceptable initial treatment threshold. As a result, a 80-140 mg/dL target was used in the 1,600 patient before-and-after interventional study³.

This experience highlights some of the important principles about successful implementation of tight glycemic control (TGC). Developing and implementing an ITT protocol is most successful where there is multidisciplinary collaboration. Before addressing TGC, nearly all routine aspects of care in the unit had been "protocolized." The nurses and physicians had experience crafting evidence-based protocols and standardized care was accepted. This was important, because TGC presented a level of complexity not present in most other protocols. Medical and nursing leadership needed to share the same vision for the unit for this work to be done successfully.

Another key point is the decision to choose an achievable goal. There was no buy-in from the nursing staff regarding the idea of TGC until they were comfortable with the glycemic target. A final component for successful execution of TGC was the availability of robust data-analysis capabilities. Clinicians who practice in the ICU need to have ready and timely access to glycemic values. The treating clinicians need to know whether hyperglycemia is being adequately controlled and whether the insulin therapy is associated with an unacceptable rate of hypoglycemia.

ICU clinicians should also have access to relevant ICU outcome data. It is not enough to know that the mean glucose level in the unit has decreased. It is also important to know if TGC had an effect on clinical outcomes, including infection rates, severity-adjusted length of stay and severity-adjusted mortality. An analysis of outcomes data from our database showed a decline in mortality within several months of initiation of the protocol. This positive feedback motivated the staff to continue doing the extra work that TGC required. The nurses knew that the protocol was having a positive effect.

Hypoglycemia and the Risk: Benefit Ratio of TGC

In the Van den Berghe surgical ICU study, severe hypoglycemia (SH, defined as glucose < 40 mg/dL) was seen in 0.8% of the conventionally treated group and 5.1% of the intensively treated group¹. In the Stamford interventional trial, SH represented 0.35% of the values in the historic era and 0.34% of the values in the treatment era². Both studies stated that the hypoglycemia that occurred in the treated patients had no adverse clinical consequences, likely due to its transient nature. Later work has refuted this view^{4,7}.

The second Leuven trial, published in 2006, was performed in 1,200 medical ICU patients⁴. The glycemic goal was 80-110 mg/dL but the monitoring was performed differently than in Van den Berghe’s earlier work. In the first study all patients had arterial lines, from which blood was sampled. In the second study only a minority of patients had arterial lines, and glycemic monitoring was done using a variety of different sources, including fingerstick capillary blood. The rate of SH in the medical ICU study was 3.1% among the control group and 18.3% among the patients in the TGC group, and the investigators noted that multivariate analysis indicated that SH mitigated the beneficial effect of intensive treatment. I believe that the high rate of SH

in the intensively treated group of the second Leuven trial explains why this study was only “equivocally positive,” instead of unequivocally positive as with their first trial.

Two other recent studies were discontinued before completion of patient enrollment and therefore can be considered failed trials, not necessarily refutations of the beneficial effect of TGC. The VISEP trial was a multi-center European trial of TGC and fluid resuscitation strategies, with a 2X2 design (creating four separate treatment groups) among patients with septic shock⁵. The final results are not available; the study was discontinued prematurely because of an excessive rate of SH in the TGC group (12.1% vs. 2.1%). The GLUCONTROL trial was another multi-center European study performed in medical and surgical ICUs⁶. The results of this study have also not been published, and it was also terminated prematurely because of unacceptable rate of protocol violations and SH.

A detailed review of the risk factors for the development of SH and the clinical consequences of SH has just been completed in a cohort of 5,365 patients admitted consecutively to our ICU⁷. Two separate analyses confirmed that a single occurrence of SH conferred increased risk of mortality. A case

control study matched 102 index cases with SH to 306 controls, using APACHE II score, age, diabetic status, diagnostic category and era of treatment (historic vs. TGC) as matching parameters. Mortality was significantly higher in the 102 patients with SH than in their 306 matched controls (Table 1). A multi-variate regression analysis controlling for these same factors yielded the same conclusion (Table 1). However, a sensitivity analysis indicated that TGC would still be beneficial even with a quadrupling of the baseline rate of SH rate and an associated doubling of the mortality percentage attributable to SH.

Recognition of the relevant risk factors is crucial to avoid deleterious SH. The most important include severity of illness, the presence of renal failure (delayed clearance of insulin), sepsis and liver failure (impaired gluconeogenesis), discontinuation of source of calories with continuation of insulin therapy and diabetes.

The rate of SH in our ICU was 0.28% among patients in the pre-TGC historic era and 0.35% among patients treated with the 80-140 mg/dL target. In January 2005, the nurses initiated a reduction in the glycemic treatment threshold to 125 mg/dL, because they were comfortable with the protocol and wanted

<p>Table 1. A Single Episode of Severe Hypoglycemia (Glucose < 40 mg/dL) Increases Risk of Mortality</p> <ul style="list-style-type: none"> • Multiple logistic regression analysis <ul style="list-style-type: none"> – Model included APACHE II score with age component deleted, age, diabetic status, septic shock, mechanical ventilation, renal insufficiency, treatment era <p style="text-align: center;">OR 2.28 (1.41 - 2.70) p = 0.0008</p> • Case: control study (1:3) <ul style="list-style-type: none"> – Matched for APACHE II score with age component deleted, age, diagnostic category, treatment era <p style="text-align: center;">Mortality rate: 55.9% vs. 39.5% p = 0.0057</p>

to decrease the threshold. This led to a significant increase in the rate of SH (0.73% of glucose values) and prompted a review the ICU database leading to the study described above. A detailed review of the individual occurrences of SH led to the recognition that when a continuous infusion was not being used, the use of regular insulin for subcutaneous “correctional” dosing was used. This was implicated in many of the instances of SH because of the potential for “dose stacking” to follow multiple administrations.

In January 2007, regular insulin for subcutaneous administration was eliminated from the protocol, replaced by fast-acting aspart analogue insulin. With monitoring performed every three hours and subcutaneous treatment given every three hours (for those patients not on continuous infusions of insulin), the rate of SH has fallen to 0.13% of values, less than half that seen during the pre-TGC historic era. Careful review of data allowed staff to recognize an important problem and track its successful resolution.

Differences Between Patients With and Without Diabetes

Another recent publication from our institution has highlighted a different impact of hyperglycemia on mortality of diabetic compared to non-diabetic ICU patients⁸. Similar findings have been noted in populations of patients with acute myocardial infarction^{9,10}. Hyperglycemia among non-diabetic patients in our ICU was a much more significant risk factor for mortality than it was among the patients with diabetes (Table 2). There are no data that report non-diabetic hyperglycemic ICU patients longitudinally to assess what percentage were “latent” diabetics or subsequently became overtly diabetic. Nevertheless, our experience highlights the importance of targeting all patients in the ICU for intensive glycemic monitoring and treatment, not just the small minority who are previously identified diabetics.

Future Directions: Advances in Monitoring and Treatment

Current standards of monitoring involve the use of a variety of different sources of blood—arterial, venous and capillary—and different measurement systems with different levels of accuracy. Considerable effort is now being expended to find a reliable continuous glucose monitor¹¹. Such a device would eliminate two important barriers to successful implementation of TGC. The work burden associated with protocol implementation would be greatly reduced. The risk of hypoglycemia would be dramatically reduced, since the nurse would have ready warning about impending hypoglycemia and be able to take corrective action. Another innovation is the automated insulin dosing tool. This device integrates clinical information, recent glucose results and recent history of insulin dosing to determine a suggested insulin dose for each successive glucose value recorded. Our nurses are empowered to make treatment decisions based on a written treatment guideline; however, insulin dosing tools might be especially useful in ICUs in which nurses do not have experience with nurse-driven protocols.

Summary

TGC has emerged as a standard of care in the ICU because of its biologic plausibility and the available interventional studies. Further corroboration may come from the ongoing NICE-SUGAR trial, a multi-center trial being conducted in Australia and Canada among more than 4,000 medical and surgical ICU patients. The success of the NICE-SUGAR trial will depend in part on whether the centers can achieve the desired glycemic goals, with clear separation of the interventional and control groups and without an unacceptable level of severe hypoglycemia. There may never be a true “historic” or “control” groups in any interventional study. It is not known whether the treatment threshold should be 110, 125, 140, or even 150 mg/dL. The depth and breadth of the currently randomized and observational data would not allow an ethical Institutional Review Board to allow a control group to maintain glucose values >200 mg/dL without treatment, as was seen in the first Van den Berghe trial.

Table 2. Mortality Associated with Mean Glucose Level During ICU Stay

5,365 patients admitted to the Stamford Hospital ICU between 10/99 and 6/06

Mean glucose during ICU	Mortality percentage		Odds ratio	
	Non-diabetics	Diabetics	Non-diabetics	Diabetics
70-99	9.2	13.0	0.45	0.45
100-119	11.3	18.9	0.67	NS
120-139	16.3	17.1	NS	NS
140-179	24.2	22.0	1.82	NS
180+	39.4	25.5	2.35	1.65

Odds ratio adjusted for age, severity of illness (APACHE II Score)

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Meta-analysis of Randomized Trials of Tight Glycemic Control

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Key points

- *The results of observational studies show that in-hospital hyperglycemia is an independent risk factor for adverse outcomes, including mortality.*
- *A single-center randomized trial found that tight glycemic control with insulin improves mortality and morbidity in the surgical intensive care unit; benefit in other hospital settings has not been established by randomized trials.*
- *Clinicians should aim for a pre-prandial glucose concentration < 150 mg/dL in most hospitalized patients, with stricter glucose goals in the critically ill patient, especially among patients with cardiac disease.*

Hyperglycemia is a common occurrence in the critically ill patient. Historically, in-hospital hyperglycemia, especially of new onset, has been seen as an adaptive response to heightened medical stress and considered a marker of illness severity rather than a distinct medical entity that requires management. Recent evidence, however, challenges that notion. Several observational studies have established that in-hospital hyperglycemia is an independent risk factor for adverse outcomes, including mortality, particularly in critically ill patients with known diabetes but also in those with new-onset hyperglycemia. Recently, several randomized trials have tested the hypothesis that lowering glycemia in hospitalized patients would improve outcomes, but with conflicting results. Here I summarize the evidence from these trials.

Early Trials

Experimentally, the concept of altering glycemia in hospitalized patients to affect outcomes was first introduced in the 1960s

when an infusion of glucose, insulin and potassium (GIK) was developed as a potential therapy to improve cardiac-related outcomes following acute myocardial infarction (AMI). Over the next 30 years multiple small intervention studies with GIK were completed with conflicting results that could be due, at least in part, to the differences in the various regimens used.

Large Intervention Studies

The first large intervention study with a glucose-insulin infusion aiming at euglycemia was the DIGAMI study, which randomized patients with diabetes and AMI to either 'routine' therapy or intensive therapy with glucose-insulin infusion for 48 hours with a glucose goal less than 10 mmol/L, followed by subcutaneous insulin therapy¹. Although there was no short-term statistically significant benefit with intensive insulin-glucose therapy, at one year the latter group had a relative mortality reduction of 26% compared to the control group.

The DIGAMI study was the first to provide concrete evidence that controlling glycemia in hospitalized patients may improve outcomes. However, it was not until 1991, when the results of a study by Van den Berghe et al. were published, that hyperglycemia and its therapy with insulin in the critically ill became of great interest to clinicians². Van den Berghe et al. conducted a randomized controlled trial where patients admitted to the surgical intensive care unit (ICU), of which 63% had cardiac surgery, received either 'routine' therapy or intensive insulin therapy (IIT) aiming at tight glycemic control (TGC). The results were remarkable: IIT resulted in a blood glucose (BG) level of 103 mg/dL vs. 153 mg/dL in the control group and significantly reduced in-hospital mortality and morbidity (see Table in Appendix).

Since then, three large studies with insulin therapy in hospitalized patients were published with neutral results.

- The CREATE-ECLA study was an international trial of patients with AMI, who were randomized upon hospital admission to receive either GIK infusion for 24 hours (without a glucose target) or usual care³. No difference on mortality or morbidity was seen with the GIK infusion.
- The DIGAMI-2 study tried to distinguish the short-term from the long-term benefits of an insulin-based glucose management protocol in patients hospitalized for AMI by randomizing patients into three groups (Table in Appendix)⁴. There were

no differences in mortality or morbidity among the three groups. This study was underpowered by not meeting enrollment numbers and did not achieve its treatment goals.

The results of the CREATE-ECLA and DIGAMI-2 trials suggest that insulin therapy without targeting euglycemia probably has no effect on outcomes.

- The third study was conducted by Van den Berghe et al. in patients in the medical ICU and followed a protocol identical to the surgical intensive care study by the same investigators⁵. Overall, there was no benefit of IIT reduced BG levels but did not significantly reduce in-hospital mortality (40% vs. 37% in the conventional vs intensive group, respectively). Among patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive therapy. In contrast, among patients who stayed in the ICU for three or more days, in-hospital mortality was reduced from 53% to 43% with IIT.

Updated Review and Meta-analysis of Randomized Trials

My colleagues and I recently conducted a systematic review and meta-analysis of randomized trials to determine the effect on mortality of insulin therapy initiated during hospitalization in patients with critical illness defined as AMI, stroke, cardiac surgery or an illness requiring a stay in the ICU⁶. I updated the search and analyses for this conference.

The search revealed 41 published randomized trials (n=32,573 patients) that have employed an insulin regimen, including GIK, and reported data on mortality. Combining results from all 41 trials, there was a trend that insulin therapy decreased short-term mortality (Relative Risk 0.94 [95% CI, 0.85-1.03]).

After combining data from studies that used a non-GIK insulin regimen, the relative risk for mortality remained essentially unchanged (Relative Risk 0.92 [95% CI, 0.74-1.15]). It is interesting to note that since the positive results in the surgical ICU reported by Van den Berghe et al. in 2001, 14 trials with a variety of insulin regimens, including GIK, in hospitalized patients have been published, and none of them have shown a statistically significant benefit for insulin therapy. Two randomized trials (VISEP and Glucontrol) whose results are pending were stopped early because of frequent hypoglycemia (these are discussed elsewhere in these Proceedings).

Conclusion

There is general agreement that improved glycemic control should be an important component of care in the hospitalized patient. Although the evidence supports TGC in cardiac patients in the surgical ICU, currently there is not enough evidence from randomized trials to recommend the same degree of strict glycemic control in all hospitalized patients. Until further evidence becomes available, it is prudent for clinicians to aim for a pre-prandial blood glucose concentration less than 150 mg/dL in all hospitalized patients, with stricter blood glucose goals in the critically ill patient, especially among patients with cardiac disease.

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Perioperative Glucose Management and IIT in the Operating Room

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Key points

- Anesthesia professionals vary in their adoption and use of intensive insulin therapy (IIT) and debate the appropriate application of intensive care unit (ICU) insulin protocols and treatment goals in patients during the pre-, intra-, and postoperative periods.
- There are very few data to answer questions such as:
 - Does tight glycemic control (TGC) during the period of surgery affect long-term patient outcomes?
 - What is the optimal glucose concentration for patients in the OR during periods of stress?
 - What is the danger of hypoglycemia for patients under general anesthesia?
- The original data from Belgium suggest substantial benefit from maintenance of blood glucose ≤ 110 mg/dL in cardiac surgery patients, but the results of subsequent studies are insufficient to mandate this level of TGC for patients in the OR.

Leaders in anesthesiology, intensive care, endocrinology, surgery, hospitalist medicine, medical genetics, nutrition, nursing, pharmacy, biostatistics, and biotechnology recognize that intensive insulin therapy (IIT) improves outcomes in select critically ill intensive care unit (ICU) patients. There are core questions that must still be resolved. For example, do ICU patients benefit most from 'tight' glycemic control (TGC) (usually defined as plasma [blood glucose] in the range 80–110 mg/dL) or 'slightly less intense' control (typically translated as blood glucose in the range 110–150 mg/dL)? Other questions include:

- What glucose concentration is the appropriate threshold to initiate treatment?
- Which IIT treatment algorithm is best (and safest)?

These questions are the same for patients in the operating room (OR) and other areas

including cardiac catheterization laboratories, neuroradiology suites, and endoscopy centers. Anesthesia professionals vary in their adoption and use of these concepts and debate the appropriate application of ICU insulin protocols and treatment goals in patients during the pre-, intra-, and post-

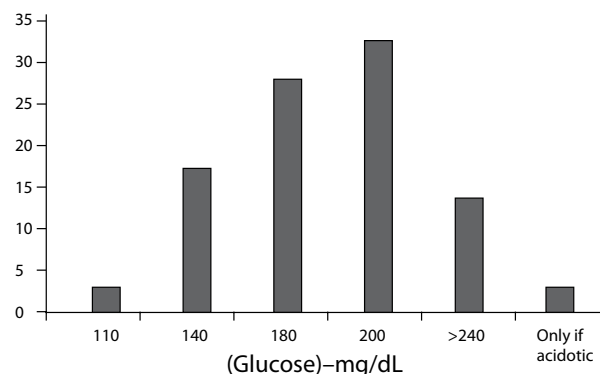
operative periods. This variation is captured in a recent web-based poll conducted by the Anesthesia Patient Safety Foundation (apsf.org), when the following question was asked:

"During general anesthesia in the OR, what is your current upper limit of glucose that triggers (intravenous bolus or infusion) insulin therapy?"

Results are illustrated in the Figure. The most common response was that insulin therapy is initiated during surgery only when patients' glucose is ≥ 200 mg/dL (11.1 mmol/L). This may surprise or even distress some ICU practitioners. Three factors may account for current practice for glucose management in the OR:

1. Lack of definitive data that IIT and TGC during surgery (a period typically lasting only two to three hours) improves perioperative outcomes, especially in subsets of patients such as ambulatory surgery patients.

Figure. Threshold that Triggers Insulin Therapy



Responses to a June, 2007 APSF poll (www.apsf.org) of anesthesia professionals asked: "During general anesthesia in the OR, what is your current upper limit of glucose that triggers (intravenous bolus or infusion) insulin therapy?"

2. The uncertainty of the ideal blood glucose target/goal in the OR (similar to the challenge and dilemma faced by ICU practitioners).
3. The ill-defined danger of iatrogenic hypoglycemia associated with IIT during anesthesia, when the classic autonomic and neurological signs and symptoms of low blood glucose are masked or absent. Implicit with this concern are the medico-legal consequences of unintended hypoglycemia during anesthesia.

Factor # 1: Does TGC during the period of surgery impact long-term patient outcomes?

There are very few data to guide glucose management for patients who are in the OR. Many anesthesia practitioners therefore question whether it is appropriate to apply data from pre-operative, post-operative, and ICU periods to the relatively brief period of surgery. Others think that data derived from studies of specific ICU populations such as those patients suffering MI, cerebral ischemia, sepsis, or undergoing cardiac surgery are not applicable to patients under general anesthesia having routine surgery lasting two to three hours. A recent prospective, randomized, open-label, controlled study at the Mayo Clinic of 400 cardiac surgery patients¹ was unable to demonstrate a benefit of IIT during surgery.

The Mayo Clinic patients were randomized to tight intraoperative control utilizing an insulin infusion to maintain blood glucose between 80–100 mg/dL while in the OR, or conventional treatment where they received insulin only when blood glucose exceeded 200 mg/dL. All patients received the “standard ICU insulin protocol” and achieved TGC within four to six hours of arrival in the cardiac ICU. Outcomes including hospital and ICU length of stay (LOS) were identical for both groups of patients. The IIT group had more deaths (4 vs. 0; $p = 0.06$), and more strokes (8 vs. 1; $p = 0.02$) than the conventional treatment group.

Although this was a modest-sized study, mortality rates were less than half that reported in the commonly discussed IIT ICU study by Van den Berghe². Van den Berghe wrote an accompanying editorial suggesting that TGC during the “brief” duration of OR care is insufficient to affect patient outcomes. Data from other studies such as the Portland Diabetic Project⁴ draw different conclusions. This non-randomized, prospective, observational study of 5,510 cardiac surgery patients found that hyperglycemia in the first three post-operative days was an independent and robust predictor of mortality, sternal wound infections, and increased LOS for patients with diabetes.

So, how do anesthesiology clinicians reconcile this conflicting information? Until conclusive data are published, some anesthesia practitioners suggest that routine glucose management is sufficient for the OR, and it is reasonable to delay TGC until the patient arrives in the ICU. They note the ICU environment is ideally suited to engage multi-disciplinary teams to implement IIT protocols.

Until then the lack of definitive evidence-based outcome data about intraoperative glycemic control will result in variable practices for insulin therapy in the OR. The core question remains as to whether two to three hours of hyperglycemia in the OR constitutes a critical risk which increases adverse patient outcomes. As this discussion continues, it is likely that intra-operative glucose management and IIT will be a component of overall perioperative care, and maybe even a benchmark for anesthesiology P4P (pay-for-performance).

Factor # 2: What is the optimal glucose concentration for patients in the OR during periods of stress?

This question parallels the challenge facing ICU practitioners. While it is widely recognized that patient outcomes improve when glucose is tightly controlled during ICU treatment for certain subsets of hospitalized patients, it is

not clear that all patients derive these benefits. An improvement has been documented in complex cardiac surgery patients for whom an aggressive IIT protocol was used for an extended time after surgery. These results have not been reconfirmed, however.

Factor # 3: What is the danger of hypoglycemia for patients under general anesthesia?

Anesthesia professionals prefer to avoid risk and are sensitive to the possibility of iatrogenic hypoglycemia when using IIT during anesthesia. The usual autonomic and neurological signs and symptoms of low blood sugar are masked or absent during anesthesia. Little is known about the frequency, severity and consequences of intraoperative hypoglycemia. Hypoglycemia in awake outpatients is defined as < 50 mg/dL in males and < 40 mg/dL in females. The clinically relevant symptoms associated with this degree of hypoglycemia are summarized in Table 1.

Clinicians are naturally cautious when conditions exist which blunt the usual responses to hypoglycemia. Drugs such as anesthetics and beta-blockers, various medical conditions, or autonomic sympathetic hypo-responsiveness (termed “hypoglycemia-associated autonomic failure,” HAAF) can blunt the physiologic response to low blood glucose, and serious neuroglycopenia can occur in the absence of changes in vital signs or observable neurological symptoms.

The concern surrounding iatrogenic hypoglycemia is one factor limiting routine aggressive glucose management in the OR. It is likely that the sequelae of hypoglycemia are duration (time)–and “dose” (severity)–related. Low glucose concentrations are associated with predictable neurological dysfunction (Table 2). There is minimal permanent risk from a single episode of hypoglycemia (blood glucose ≤ 40 mg/dL), providing it is diagnosed and managed in a timely fashion. A recent study⁵ of a long-term, outpatient, intensive diabetic-care algorithm showed that patients experi-

Table 1: Signs and Symptoms of Hypoglycemia in Awake Patients

Behavior/mood alterations

- Emotional lability
- Irritability

Physical Symptoms

- Diaphoresis
- Tremor
- Paresthesia
- Tachycardia

Neuroglycopenic Signs and Symptoms

- Hypothermia
- Weakness
- Fatigue
- Slurred speech
- Loss of consciousness (LOC)
- Hemiparesis
- Seizures
- Brain damage

enced frequent hypoglycemic episodes. The extensive battery of neuropsychiatric tests, however, found no difference in neurological deficits between intensive and routine diabetic care for study patients. In nearly two decades, no adverse neurological sequelae could be correlated with hypoglycemic episodes.

More data are needed to define the minimal duration and severity of hypoglycemia that constitutes “neurological risk” for patients in the OR (where brain temperature may be an important co-variate, for example). This information will define the optimal time increment between blood sugar determina-

tions for patients who are receiving IIT under general anesthesia. This is important because additional variables such as blood sampling site (venous vs. capillary vs. arterial), anemia, and confounding substrates may lead to spurious glucose determinations⁷.

A Summary of Perioperative Glucose Management

Conclusions about perioperative glucose management include:

- The prevalence of type 2 diabetes mellitus is increasing rapidly.
- TGC requires an interdisciplinary team approach, a culture of safety and a focus on professional education. Benchmarks to evaluate effectiveness are needed.
- It is important to note that perioperative hyperglycemia occurring in “non-diabetics” may actually indicate undiagnosed type 2 diabetes that may result in increased morbidity and mortality. Providers should consider hemoglobin A1c determinations in these patients to direct optimal metabolic management and potentially alter the timing of procedural intervention, particularly for elective surgeries such as joint replacement, spine surgery or bariatric procedures.
- It is now being recognized that insulin is appropriate therapy for all acute stress and perioperative hyperglycemia. The treatment of patients who do not have diabetes but become hyperglycemic may achieve the greatest benefit with appropriate treatment.

• Clinical experience suggests that a single episode of hypoglycemia (blood glucose ≤ 40 mg/dL) carries minimal risk if diagnosed and managed in a timely fashion. The issue of hypoglycemia is still a concern for the many anesthesia professionals. Patients with sepsis exhibit a much higher risk of hypoglycemia and control of their blood sugar is more difficult.

• Practitioners in both the OR and ICU struggle with the question of what is the necessary, appropriate and “ideal” glucose target. The original cardiac surgery data from Leuven, Belgium suggest substantial benefit from maintenance of blood glucose ≤ 110 mg/dL. Current data appear insufficient to mandate this level of TGC for patients in the OR. A recent randomized study in cardiac surgery patients found no difference in ICU or hospital LOS despite TGC throughout the operative period.

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Table 2: Neurological Consequences of Hypoglycemia

Blood sugar below 45 mg/dL = neuroglycopenia

- Altered mentation, eventually leading to seizures, unconsciousness and coma

Below 36 mg/dL = EEG changes

- EEG changes persist even after restoration of plasma sugar

Below 18 mg/dL = neuronal necrosis likely

PROCEEDINGS

Economic Advantages of Tight Glycemic Control

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Key points

- *Measures of importance in evaluating the economic impact of tight glycemic control (TGC) include clinical outcomes, mortality and morbidity, reduction in length of stay, equipment utilization and personnel time.*
- *Studies have shown that achieving TGC reduces intensive care unit-related complications and length of stay compared with conventional glycemic management that produces higher mean glucose values of 150-170 mg/dL.*
- *The degree of cost saving may vary with other patient populations and with other glycemic management programs, depending on the baseline complication rate and the effectiveness and safety of the TGC protocol; however, outcome and economic benefits of TGC appear to be significant and positive.*

Evaluation of the economic impact of any intervention in the critical care unit is a complex proposition. Many overhead expenses are fixed in a technology-rich environment. However, there have been several reports examining the potential impact of tight glycemic control (TGC) in critical care.

The economic measures of importance include clinical outcomes, mortality and morbidity, length of stay, equipment utilization and personnel time. A reduction in mortality is the most important clinical outcome; however, it can lead to additional expenses if associated with a longer intensive care unit (ICU) length of stay (LOS) or additional therapeutic interventions. The large trials of tight TGC have also demonstrated significant reductions in morbidity^{1,2}.

The two large clinical trials from Leuven, Belgium demonstrated significant absolute

mortality reduction of at least 3% to 4% in all patients and above 7% in surgical intensive care (SICU) patients and medical ICU (MICU) patients who remained in the ICU for more than 3 days³. A combined dataset from these two trials demonstrated consistent benefits in all subsets with the exception of patients with diabetes who were previously treated with insulin, where a tendency toward increased risk of death was suggested. While the benefit on mortality may be progressive as the glucose is lowered to normal ranges of 80-110 mg/dL, achieving normoglycemia appears essential to prevent renal failure and critical-illness polyneuropathy⁴.

Specific morbidity measures have great impact on cost analysis. TGC reduced ICU and hospital LOS and, importantly, reduced the percentage of patients requiring more than two weeks of ICU care¹. Reduction of the duration of mechanical ventilation (MV)

and the need for prolonged ventilation is an important contributor to more rapid ICU discharge. The need for MV has a large impact on ICU costs, as demonstrated by Dasta and colleagues⁵. Mean intensive care costs and LOS were higher than for those not requiring MV. Daily costs were greatest on day 1 (\$10,794 versus \$6,667 for MV vs. no MV, respectively) and decreased daily, becoming stable after day 3 (\$3,968 vs. \$3,184, respectively). The mean incremental cost of MV was \$1,522 per day, although costs appear to be higher in surgical and trauma patients than in medical ICU patients.

Infectious complications are another important contributor to hospital costs. The importance of glucose control has been shown by the Portland Diabetic Project. Reductions in the three-day post-operative average blood glucose (3BG) have been associated with progressive reductions in deep sternal wound infection (DSWI) and mortality⁶. The risk of post-cardiac bypass mortality is doubled for each 50mg/dL increase in 3BG. The reported 3.2% reduction in DSWI translates into a number needed to treat (NNT) of 31 diabetic patients to prevent 1 DSWI. The cost of a DSWI was reported to be \$81,000⁷. The average cost per day in open heart surgery patients has been reported to be as high as \$1,150⁸. In summary, actual cost saving per patient is \$2,613 and savings from reduced length of stay is \$3,150 per day, producing a net saving of \$5,580 (\$138-\$5,718) per patient treated with the Portland Protocol⁶.

Cost savings are also associated with prevention of other complications such as blood stream infections (BSI) and renal failure. The Leuven SICU study with TGC demonstrated significant reductions in ICU septicemia and the number of patients who are treated with more than 10 days of antibiotics¹. The attributable costs of an ICU-acquired BSI are substantial and vary from approximately \$9,400 to \$18,000 (Table 1). The impact from avoidance

economic impact of a therapeutic intervention is essential. The Leuven SICU study produced significant reductions in mortality and morbidity related to reductions in septicemia, renal failure, red-cell transfusions, need for drug therapy (pressors, antibiotics, inotropes) and development of critical illness (polyneuropathy). The comprehensive cost analysis included bed, therapy and monitoring costs (Table 2)¹⁶. The costs for insulin therapy and

ferences in total cost per patient was 7,931€ (6,746-9,031€) for the TGC group vs. 10,569€ (9,214-11,441€) for the conventional treatment group. This translates into a savings of 2638€ (183-4,695€) per patient or approximately \$3,429.

A similar analysis was performed in a community-based medical-surgical ICU based on the results of a before-and-after comparison of cohorts¹⁷. The historical cohort did not have a focused glucose management program, while the after cohort was managed to achieve blood glucose of 80-140 mg/dL. The glucose management protocol resulted in a significant reduction in outcome measures, including a 13.9% reduction in ICU days and a 34.3% relative reduction in the duration of MV. These positive results produced a net cost savings per patient of \$2,311 or an adjusted saving of \$1,580 when correcting for differences in ventilation at baseline. These savings considered hospital costs, imaging, pharmacy, laboratory, and the higher costs for intensive insulin therapy, but do not account for every ICU cost. An annualized, adjusted total cost savings was predicted to be \$1,339,500 with the application of TGC in a 14-bed unit.

Table 1. Attributable Costs Reported Per Acquired Blood Stream Infection

Country	Cost	Approx. US Cost
Canada ⁹		\$7,885 per case \$16,099 per survivor
Italy ¹⁰	€16,356 per case €13,611 per survivor	\$17,694 per survivor
Belgium ¹¹	€ 13,585 per case	\$17,661 per case
USA ¹² Missouri		\$11,971 per case Severity adjusted
USA ¹³ Pittsburgh		\$40,179 per case \$9,419-\$170,565

Ratio € to US of 1:1.3 applied, if not reported in the paper

of renal failure and the need for renal replacement therapy is also potentially important. The Leuven group reported that maintaining TGC (80-110 mg/dL) was essential to prevent renal impairment and produced an overall 42% risk reduction ($p=0.0009$) versus conventional glucose control⁴. The cost of continuous veno-venous hemofiltration (CVVH) has been reported to be approximately \$390 per 24 hours (\$292 to \$488)⁹.

A potential drawback to the use of TGC is the impact on nursing workload. This is an important component of analysis, considering the fixed number of critical care nurses. A detailed discussion of the impact on workload is available from Aragon in this summary¹⁵.

While avoiding individual complications is important, an overall assessment of the

monitoring were 72€ (approx. US \$93.60) higher in the TGC group. However, the dif-

Table 2. Expenses Associated With Tight Glycemic Control¹⁶

Variable	Cost, €	Cost Approx. US\$
ICU length of stay (per day)	1030.00	1339
Mechanical ventilation (per day)	40.80	53.04
Hemodialysis (per day)	386.00	501.80
IV tubing (changed daily)	4.77	6.20
IV pump (per day)	4.75	6.18
0.9% NaCl for in injection	1.20	1.56
Regular Human Insulin (per unit)	0.03	0.04
Whole blood glucose measure	0.90	1.17

US = 1.3 x €, if not reported in the paper

Conclusion

Achieving TGC has been shown to reduce ICU-related complications and LOS compared with conventional glycemic management that produces higher mean glucose values of 150-170 mg/dL. The degree of cost saving may vary with other patient populations and other glycemic management programs, depending on the baseline complication rate and the effectiveness and safety of the TGC protocol, but outcome and economic benefits of TGC appear to be significant and positive.

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Intensive Insulin Therapy in the Intensive Care Unit

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Key points

- *New approaches, algorithms and tools are necessary to achieve tighter glycemic targets without substantially increasing the risk of harmful hypoglycemic events.*
- *Use of a protocol at Atlanta Medical Center (AMC) led to better overall blood glucose control in the intensive care unit, hypoglycemia episodes less than 1% of blood glucose measurements and infrequent episodes of sustained hypoglycemia.*
- *The average blood glucose level declined for all hyperglycemic patients whether or not the physician ordered constant insulin infusion per the protocol.*
- *AMC experience showed that:*
 - *Tight glycemic control (TGC) initiatives must be nurse-driven with the support of a physician champion and hospital administration.*
 - *Successful implementation of TGC requires much more than just a good insulin-infusion protocol.*
 - *Minimizing prolonged hypoglycemia is imperative.*
 - *Measuring the impact of new approaches on average blood glucose measurements and outcomes is important.*
 - *Computerized systems to automate calculation and documentation are needed to reduce nurse workload and facilitate compliance.*
 - *A successful program requires a change in thinking at many levels within the organization and takes longer than expected.*

Although there is still disagreement about the appropriate target for glycemic control, current evidence suggests that for patients in the intensive care unit (ICU) peak blood glucose should be lower than traditionally allowed. Studies from Van den Berghe¹⁻³, Furnary⁴⁻⁵, and Krinsley⁶⁻⁸ suggest the target may be as low as 80-110 mg/dL. Others are studying whether blood glucose levels as high as 180 mg/dL are acceptable, especially

in the medical ICU⁹⁻¹⁰. Regardless of the target range finally agreed upon, new approaches, algorithms and tools are necessary to achieve tighter glycemic targets without substantially increasing the risk of harmful hypoglycemic events.

Diabetes Special Interest Group

The Partnership for Health and Accountability (PHA), supported by the

Georgia Hospital Association, saw tight glycemic control (TGC) as an issue involving quality of care and patient safety that confronted a large number of Georgia Hospitals. In 2003, the Diabetes Special Interest Group* (DSIG) was organized as a part of the PHA, paralleling similar efforts in other parts of the country¹¹. Nurses at the Atlanta Medical Center (AMC) ICU, a 50-bed, open ICU with medical, surgical, coronary, trauma and open-heart surgery patients, were concerned about the variability in average daily blood glucose levels and frustrated by the wide variety of approaches to treatment. A multidisciplinary Glucose Control Team (GCT) was formed and concluded that a standardized approach was needed to reduce confusion among the nurses who administered glucose control orders. GCT nurses participated in the DSIG and decided to pilot test the group's work product as an evidence-based approach to TGC.

Developing and Implementing the DISG Protocol for TGC

For more than two years, the DSIG held monthly meetings that involved well over a hundred different people representing at least 50 hospitals and other organizations interested in improving inpatient glycemic control in Georgia hospitals. The group reviewed 12 protocols, which showed wide variability in insulin-dose recommendations¹². Several years' work by the DSIG produced the colum-

* The history and work of the DSIG can be viewed on the PHA/DSIG webpage at <http://diabetes.gha.org>.

nar insulin dosing chart shown in Figure 1. The decision rules were first published by Steed, Bode and Davidson¹³⁻¹⁴ describing an early computerized version that became the Glucommander®.

The chart may appear more complicated than a calculation method, but most nurses can use it after an hour of instruction. The numbered columns in the chart represent a series of parallel correction scales with different conversion factors. The most highly insulin-sensitive patients will be controlled using the information in column one. Recommendations for the management of patients with progressive degrees of insulin resistance are represented in the higher-numbered columns to the right. The DSIG web-page has a second chart for more resistant patients (typically ICU patients who are have an infection, are obese and/or are being given glucocorticoids). The left column and the color codes provide decision rules that change with the blood glucose level.

This method requires hourly fingerstick blood glucose tests until the patient stabilizes. When this occurs the interval between blood glucose checks can be lengthened to two hours. The chart includes recommendations for correction of “below target” blood glucose levels using 50% dextrose. The lower target is set at 80 mg/dL, well above the AMC “hypoglycemic threshold” of 60 mg/dL. Sustained hypoglycemia is rare, because of the frequent blood glucose checks, drip-rate adjustments as needed and below-target corrections with 50% dextrose.

While an effective algorithm, chart or computer program is necessary, more is needed to safely achieve the TGC target currently believed necessary to reduce hyperglycemia-related complications. Few treatment schemes are as complex as an insulin-dosing regimen for TGC with minimum hypoglycemia. This complex regimen must be integrated into the workload of a modern, very busy ICU in which multiple treatments are given and multiple parameters monitored.

The nurse is responsible for implementing the treatment plan. Every attempt should be made to make a treatment algorithm as user-friendly as possible. Nurses should lead this effort or at least be integrally involved.

Several steps were important to the successful IIT implementation at AMC (Table). To reduce the confusion with the many approaches, the interdisciplinary team chose a single approach from those available. After the protocol was determined to be suitable, nurses were trained and a pilot test was conducted. This allowed staff to detect unanticipated barriers before proceeding with general implementation. Following a successful pilot, the protocol was implemented as standard policy through the normal medical staff policy-making system. The protocol then was well publicized within the institution. Major factors for success are education, education and education.

Results

After a successful AMC pilot test, full implementation of the protocol led to better overall blood glucose control in the ICU, although for a variety of reasons the target range is not always reached during the first 24 hours. The number of hypoglycemia episodes as a percent of blood glucose measurements of patients receiving insulin infusions is significantly less than 1% and sustained hypoglycemia is rare.

Our experience has been that when staff focused on blood glucose control, the average glucose level declined for all hyperglycemic patients, regardless of whether or not the physician ordered constant insulin infusion using the “Columnar Dosing Chart” (Figure 3). This is a good demonstration of the “Hawthorne Effect” observed by social scientists in the 1930s (performance improves when workers know it is being measured)¹⁶. The mean blood glucose in the constant insulin infusion group is higher than the blood glucose targets for several reasons: 1) a delay in instituting the

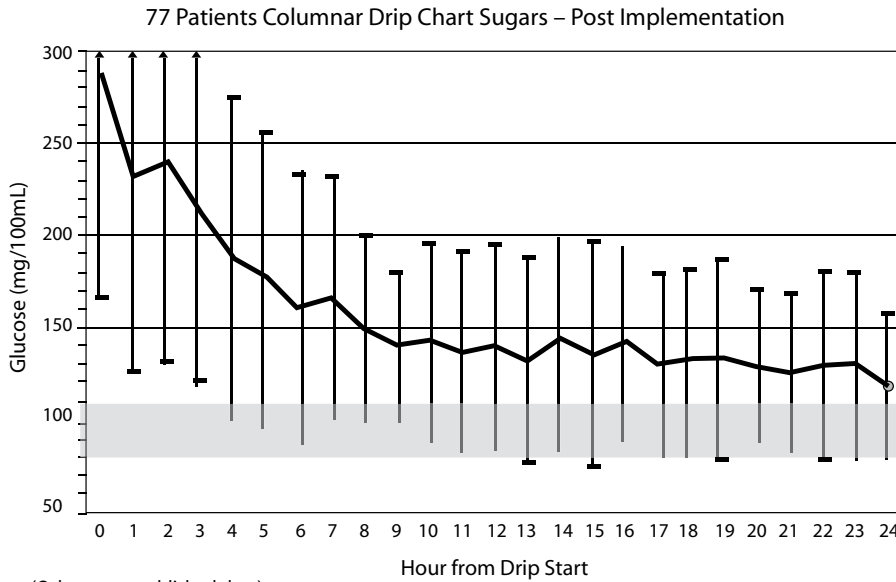
Figure 1. PHA/DSIG Columnar Insulin Dosing Chart*

DIRECTIONS		TARGET BG 80-110 (1ML = 1 UNIT)															
		Columnar Insulin Dosing Chart*															
Blood Glucose Tests (mg/dL)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
To determine the new drip rate, compare a current BG with the previous BG. Use:	Over 450	4.4	8.8	13.2	17.6	22	26.4	30.8	35.2	39.6	44	48.4	52.8	57.2	61.6	66	70.4
If current BG is lower than the previous BG then STAY IN THE SAME COLUMN	385-450	3.6	7.2	10.8	14.4	18	21.6	25.2	28.8	32.4	36	39.6	43.2	46.8	50.4	54	57.6
If current BG is lower than the previous BG then MOVE TO THE RIGHT	334-384	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
If current BG is lower than the previous BG then MOVE TO THE RIGHT	290-333	2.5	5	7.5	10	12.5	15	17.5	20	22.5	25	27.5	30	32.5	35	37.5	40
If current BG is lower than the previous BG then MOVE TO THE RIGHT	251-289	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21	23.1	25.2	27.3	29.4	31.5	33.6
If current BG is lower than the previous BG then MOVE TO THE RIGHT	217-250	1.7	3.4	5.1	6.8	8.5	10.2	11.9	13.6	15.3	17	18.7	20.4	22.1	23.8	25.5	27.2
If current BG is lower than the previous BG then MOVE TO THE RIGHT	188-216	1.4	2.8	4.2	5.6	7	8.4	9.8	11.2	12.6	14	15.4	16.8	18.2	19.6	21	22.4
If current BG is lower than the previous BG then MOVE TO THE RIGHT	163-187	1.2	2.4	3.6	4.8	6	7.2	8.4	9.6	10.8	12	13.2	14.4	15.6	16.8	18	19.2
If current BG is lower than the previous BG then MOVE TO THE RIGHT	141-162	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
If current BG is lower than the previous BG then MOVE TO THE RIGHT	121-140	0.8	1.6	2.4	3.2	4	4.8	5.6	6.4	7.2	8	8.8	9.6	10.4	11.2	12	12.8
If current BG is lower than the previous BG then MOVE TO THE RIGHT	111-120	0.6	1.2	1.8	2.4	3	3.6	4.2	4.8	5.4	6	6.6	7.2	7.8	8.4	9	9.6
When newly 80 or less, use in the same column to determine the new drip rate.	106-110	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8
When newly 80 or less, use in the same column to determine the new drip rate.	101-105	0.4	0.9	1.3	1.8	2.2	2.7	3.1	3.6	4	4.5	5	5.4	5.8	6.3	6.7	7.2
When newly 80 or less, use in the same column to determine the new drip rate.	96-100	0.4	0.8	1.2	1.6	2	2.4	2.8	3.2	3.6	4	4.4	4.8	5.2	5.6	6	6.4
When newly 80 or less, use in the same column to determine the new drip rate.	91-95	0.3	0.7	1	1.4	1.7	2.1	2.4	2.8	3.2	3.5	3.8	4.2	4.6	4.9	5.3	5.6
When newly 80 or less, use in the same column to determine the new drip rate.	86-90	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3	3.3	3.6	3.9	4.2	4.5	4.8
When newly 80 or less, use in the same column to determine the new drip rate.	80-85	0.2	0.5	0.7	1	1.2	1.5	1.7	2	2.3	2.5	2.7	3	3.2	3.5	3.7	4
When newly 80 or less, use in the same column to determine the new drip rate.	75-79	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2	2.2	2.4	2.6	2.8	3	3.2
When newly 80 or less, use in the same column to determine the new drip rate.	71-74	0.1	0.3	0.4	0.6	0.7	0.9	1	1.2	1.3	1.5	1.7	1.8	1.9	2.1	2.2	2.4
When newly 80 or less, use in the same column to determine the new drip rate.	60-70	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6
When newly 80 or less, use in the same column to determine the new drip rate.	Under 60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

BG	INSULIN	ACTION	NOTICE PROMPTLY IF:
78-79	10 ml IV Push	If you have not moved 1 column to the left as directed above, do so now	2 BG is less than 80 for 2 consecutive BG measurements
76-77	15 ml IV Push	Recheck BG in 15 minutes	3 BG is less than 80 for 3 consecutive BG measurements
74-75	20 ml IV Push	Repeat as necessary	4 BG is less than 80 for 4 consecutive BG measurements
72-73	25 ml IV Push	If you have not moved 1 column to the left as directed above, do so now	5 BG is less than 80 for 5 consecutive BG measurements
70-71	30 ml IV Push	Recheck BG in 15 minutes	6 BG is less than 80 for 6 consecutive BG measurements
68-69	35 ml IV Push	Repeat as necessary	7 BG is less than 80 for 7 consecutive BG measurements
66-67	40 ml IV Push	Contact physician if BG is under 80 for 2 consecutive BG measurements	8 BG is less than 80 for 8 consecutive BG measurements
64-65	45 ml IV Push		9 BG is less than 80 for 9 consecutive BG measurements
62-63	50 ml IV Push		10 BG is less than 80 for 10 consecutive BG measurements
60-61	55 ml IV Push		11 BG is less than 80 for 11 consecutive BG measurements
58-59	60 ml IV Push		12 BG is less than 80 for 12 consecutive BG measurements
56-57	65 ml IV Push		13 BG is less than 80 for 13 consecutive BG measurements
54-55	70 ml IV Push		14 BG is less than 80 for 14 consecutive BG measurements
52-53	75 ml IV Push		15 BG is less than 80 for 15 consecutive BG measurements
50-51	80 ml IV Push		16 BG is less than 80 for 16 consecutive BG measurements

Copies of this chart can be downloaded at no charge at from www.diabetes.gha.org.

Figure 2. Blood Glucose Measurements Post-implementation of Standardized Protocol for TGC



Any attempt to achieve TGC requires an investment of time and resources. While published studies demonstrate a return on investment based on shorter stays, reduced infections, and reduced mortality, the debate still surrounding TGC creates doubt in the mind of administrators asked to fund the cost. TGC requires more frequent blood glucose checks and hence more bedside glucose monitors and increased use of related consumable supplies. Blood glucose checks, algorithm-related nurse decisions and nurse documentation will add 30 to 45 minutes per shift of nurse work time. Our hospital is like many others in its lack of sophisticated outcomes-tracking systems. This makes it difficult to observe and document the benefits of TGC. The increased costs are very noticeable and will result in questions and requests for justification from the finance staff in the hospital.

infusion, 2) premature termination of the infusion when glycemic targets were reached (while the patient still had fluctuating insulin sensitivity because of other active problems), and 3) poor transition to subcutaneous insulin once a decision was made to discontinue constant insulin infusion.

Lessons Learned

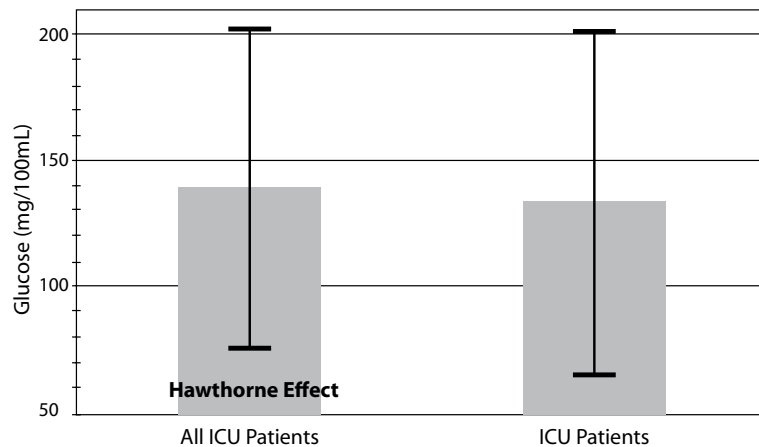
Implementation of TGC at AMC was successful and educational. The following lessons were learned.

- Nurses must be the principal drivers since the work required falls most heavily on their shoulders.
- A physician champion is important for support and representation to the physician staff. Key physicians in the ICU must be recruited early and educated to reduce the effects of fear of hypoglycemia, increase understanding of the benefits of TGC and minimize the effects of clinical inertia.

- Despite considerable, consistent effort on the part of the GCT, acceptance comes slowly.
- Constant reeducation is needed.
- A dedicated, nurse-expert GCT is important to sustaining the effort required to change.

The requirement for hourly fingerstick blood glucose determinations is one of the major hurdles to nurse acceptance of safe TGC efforts. Frequent blood glucose determinations minimize the risk of sustained hypoglycemia. Transient blood glucose decreases below 60, 50, or even 40 mg/dL rarely cause long-term harm, although they are likely to be uncomfortable for the patient. Sustained

Figure 3. Raw Average Blood Glucose for Entire ICU Stay



hypoglycemia is to be avoided because of the risk of central nervous system damage or even death. A low incidence of sustained hypoglycemia with the use of TGC treatment strategies builds confidence and hence physicians' and nurses' support. Intermittent feeding such as meals or bolus tube feeding compromises the impact of currently published algorithms, and these feedings should be avoided for patients requiring insulin infusion for TGC.

Transition to subcutaneous (SC) insulin. A successful inpatient TGC plan requires a good system for the transition to an effective basal-bolus SC insulin therapy regimen. Transition from the insulin infusion algorithm is as least as difficult as execution of the insulin infusion algorithm, and there is not much published information about this. Transitioning patients is one reason why the raw mean blood glucose level in the AMC ICU is not as close to target as desirable.

While there are multiple published insulin infusion protocols and at least two FDA-approved computerized systems, there is no published study of head-to-head comparisons of various protocols in a clinical setting. There is little published experience using protocols for transition from IV insulin infusion to basal-bolus SC regimens. Basal-bolus regimens should be used in patients able to take oral feeding. Finally, debate continues on the appropriate target ranges for TGC should be outside of the cardiac surgery ICU setting.

Conclusions

Based on the experience at AMC, the following key factors affect implementation of TGC in the ICU:

- TGC initiatives must be nurse-driven with the support of a physician champion and hospital administration.
- Successful implementation of TGC requires much more than just published articles and a good insulin-infusion protocol.
- Minimizing prolonged hypoglycemia is imperative.
- Measuring the impact of new approaches on average blood glucose measurements and outcomes is important.
- Computerized systems that automate calculation and documentation are needed to reduce nurse workload and facilitate compliance.
- A successful program requires a change in thinking at many levels within the organization and takes longer than expected.

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Use of a Computerized Algorithm in Patients Undergoing Cardiovascular Surgery: A Protocol for Tight Glycemic Control

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Key points

- Hospital protocols to control glucose must be simple and user-friendly.
- These protocols should allow patients with hyperglycemia to be treated the same, allowing modification and refinement of the protocol only when necessary.
- There are two effective methods for normalizing glucose for hospitalized patients: continuous, variable-rate intravenous (IV) insulin infusions and basal bolus subcutaneous (SC) insulin therapy
- Computerized algorithms for IV insulin infusion and transition to SC insulin therapy enable standardization that can minimize medical errors made in insulin dosing.
- The use of a computerized protocol for cardiovascular surgery patients resulted in near-normal glycemia (mean blood glucose 107 mg/dL) with no blood glucose < 40 mg/dL.

Introduction

Studies have shown the benefits and risks of tight glycemic control (TGC) in hospitalized patients, including the intensive care unit (ICU)¹⁻⁴. TGC methodologies can be difficult to implement because they often require complex, insulin-dosing formulas that are restricted to the ICU, and highly skilled nurses to work with only one or two patients at a time. Severe hypoglycemia also can be a problem with many intravenous (IV) insulin protocols and has been shown to be an independent risk factor for mortality⁵. In this article, the methodology, results and benefits of a computerized protocol in cardiovascular (CV) patients undergoing bypass or valve surgery are discussed.

The recommended goals for glyce- mic control in the hospital vary slightly between the American Association of Clinical Endocrinologist (AACE) and the American

Diabetes Association (ADA). Both organi- zations recommend a blood glucose level < 110 mg/dL in the ICU. AACE recommends < 110 mg/dL premeal with peak postprandial < 180 mg/dL, while the ADA recommends 90-130 mg/dL premeal⁶.

To accomplish these goals while minimiz- ing the risk of hypoglycemia, protocols can be developed and implemented to screen patients at high risk for hyperglycemia and to modify and initiate insulin therapy when needed. If a patient is acutely ill or unable to eat, a continuous, variable-rate IV insulin infusion based on hourly or more frequent glucose measurements should be used. If a patient is stable and able to eat, subcutane- ous (SQ) basal bolus therapy can be used, with blood glucose measured premeal, at bedtime and at 0300. Transition from IV to SC basal bolus insulin therapy should be done with known or newly diagnosed patients

with diabetes who had pre-existing glycemia based on an A1c > 6%. Discharge planning should be done for all patients with diabe- tes who have not received insulin before, including those who are newly diagnosed. Case-specific recommendations are made for diabetes management at home.

Methodology

Based on the above goals, Piedmont Hospital in Atlanta decided to implement a TGC protocol in CV patients undergoing bypass and valve surgery. This decision was made after analysis of data from the preced- ing six months that revealed that only 50% to 60% of CV patients had met the Institute for Healthcare Improvement's goal of having all blood glucose levels be < 200 mg/dL in the 24 hours post-surgery⁷. To achieve this goal, a team of endocrinologists, nurses, pharma- cists and educators met with a CV surgeon every week for three months to develop the protocol. All parties agreed to the following:

1. The protocol would be used for all patients, so that all patients would be treated the same.
2. Since CV patients are at high risk for hyper- glycemia, upon arrival at the hospital all patients would be screened for both A1c and glucose.
3. If a patient were admitted > 24 hours before surgery, a weight-based basal bolus SQ insulin would be initiated if the A1c were > 6% or the premeal blood glucose was > 140 mg/dL. The weight-based for-

mula used in the protocol is weight in Kg times 0.5 equals total daily dose ($Kg \times 0.5 = TDD$), with 50% of the basal being given as glargine insulin at bedtime and the remaining 50% of insulin divided by 3 and given as a pre-meal dose of rapid-acting insulin (RAI). Bedside capillary blood glucose would be measured premeal, at bedtime and 0300, with a correction dose of RAI given for a blood glucose > 140 mg/dL. The correction formula would be blood glucose minus 100, divided by correction factor as determined by the 1700 rule, which is 1700 divided by the TDD ($[\text{blood glucose} - 100] / [1700/TDD]$).

4. Within the the 24-hour period pre-surgery through the peri-operative period, computerized IV insulin delivery using Glucomander® would be initiated for anyone with one blood glucose > 140 mg/dL or two blood glucose > 110 mg/dL⁸. Targets for glucose control would be 90-120 mg/dL with blood glucose measurement in response to a Glucomander® alert (average, hourly; range, every 20 to 120 minutes based on the stability of the glucose). The lower alert target of 90 mg/dL was selected to minimize the risk of hypoglycemia. Maintenance intravenous fluids (IVFs) are administered using D10W at 50mL/hr to prevent catabolism and allow a 1-to-1 conversion of IV units to SC units.
5. Hypoglycemia (< 60 mg/dL) would be treated with 50% Dextrose IV, based on the following formula: $(100 - \text{blood glucose}) \times 0.4 = \text{mL of D50 IV push}$.
6. IV insulin therapy would be continued until the morning of postoperative day (POD) #2 and longer if a patient were unable to eat or still critically ill. Transition to SC basal bolus therapy would be done only if the patient had known diabetes or an A1c $> 6\%$. The transition is initiated by giving glargine insulin at 11p.m. POD #1 if the

patient is stable, with RAI given premeal the following morning and stopping of the IV insulin and IVFs post-breakfast. The TDD was calculated by using the multiplier on the Glucomander® at 11 p.m. the night of transition, with the glargine dose being 500 times the multiplier, the RAI dose being the same dose divided by 3 and given in proportion to the food consumed, and the correction dose given as listed in the weight-based formula. Insulin SQ doses would be adjusted by 20% if blood glucose readings were outside the 70-140 mg/dL range. Diet therapy would be initially 1800 Kcal ADA diet in all patients with adjustment based on nutrition consultation.

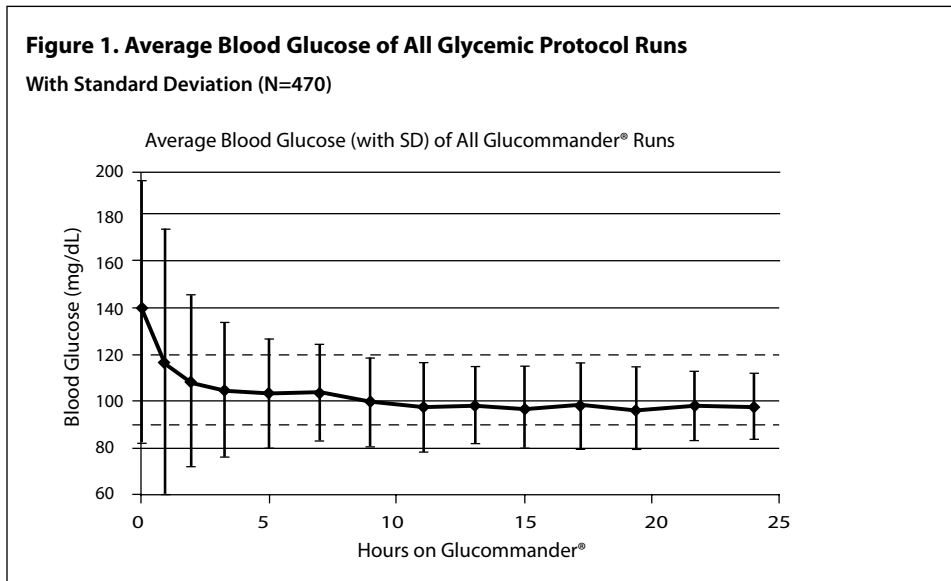
7. Discharge planning and diabetes education would be provided for all patients who have not self-administered SQ insulin and patients with a change in their insulin regimen. All patients with A1c $> 7\%$ would be instructed to remain on their basal bolus insulin therapy for at least 4 to 6 weeks or longer, until advised otherwise by their primary care practitioner.
8. An endocrinologist would be consulted for any patient with a blood glucose < 70 or > 140 mg/dL or a patient who had not received insulin before.

Results:

The above protocol was initiated in January 2006 with a one-month pilot followed by use for all patients in February 2006. As of October 2006, more than 1,800 patients have been treated using this protocol. Data from the first 470 patients were analyzed, producing the following results.

1. 28% of patients had pre-existing diabetes with 10% of all patients being on insulin pre-admission; 48% of patients had an A1c $> 6\%$ with 52% having one or more of these three criteria.
2. 96% of patients needed IV insulin peri- and post-operatively with the time to < 120 mg/dL being 3 hours. IV insulin was continued for a mean of 37 hours. Mean blood glucose was 107 mg/dL with 2% of patients having a transient blood glucose < 50 mg/dL and no patient having a blood glucose < 40 mg/dL (Figure 1).
3. 98% of patients have been controlled with no blood glucose > 200 mg/dL within the first 48 hours postoperatively.
4. 55% of patients were transitioned to basal-bolus therapy whereby $> 90\%$ of the blood glucose values remained in the target range (70-140 mg/dL) with no blood glucose < 40 mg/dL (Figure2).

Figure 1. Average Blood Glucose of All Glycemic Protocol Runs With Standard Deviation (N=470)



5. 23% of patients were discharged with home insulin therapy: > 90% of those were discharged on basal-bolus therapy.
6. Nursing feedback after the first 60 days was uniformly positive: the only major initial complaint was the frequency of glucose monitoring while a patient is on IV insulin. Complaints subsided after nurses realized that patients had fewer infections and shorter length of stay. Agency and float nurses were able to learn the protocol within their first shift on the CV ICU post-operative unit or CV floor.
7. Physician acceptance of the protocol has been uniformly positive with no criticisms or complaints.
8. Post-operative length of stay was reduced by 0.8 days for an estimated annual savings of over > \$800,000.

Conclusions

This glycemic protocol using a computerized system for IV insulin infusion and transition to SC basal bolus insulin therapy was highly effective in normalizing blood glucose without significant hypoglycemia in all patients undergoing CV surgery at Piedmont Hospital in Atlanta. Several important factors

were involved in achieving this success. The protocol was designed and implemented as a group effort by diabetes specialists, nurses, pharmacists and educators under the guidance of a CV surgeon who championed the program to his fellow surgeons and hospital administration. Empowerment of the nurses in the design, ownership and implementation of the protocol was crucial. Use of a proven, computerized, IV-insulin-dosing algorithm (Glucommander®) with appropriate setting of the target range of 90-120 mg/dL allowed all patients to obtain a mean glucose of 107 mg/dL with no glucose < 40 mg/dL.

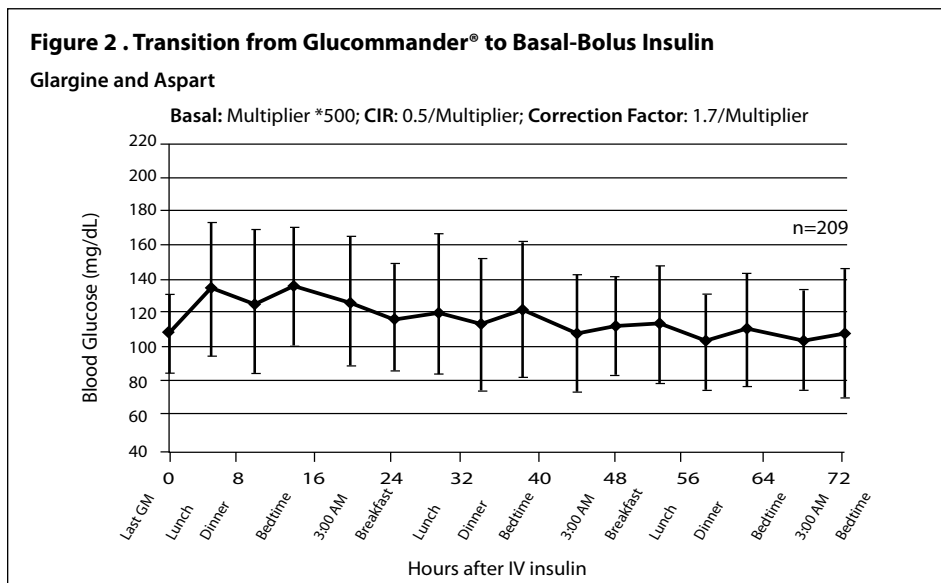
Transition from IV to SQ insulin in all patients with known diabetes or an A1c > 6% allowed normalization of blood glucose after eating during the post-operative period until discharge. To accomplish this, all patients were screened for diabetes and had an A1c drawn to identify patients to transition from IV to SQ insulin and who would benefit from insulin after discharge. Any patients admitted with poorly controlled diabetes were normalized in the hospital with insulin and discharged with an insulin regimen to keep their blood glucose levels normal as long as they complied with their case-specific regimen. It is felt by all

team members that such a glycemic protocol could also be used in normalizing glucose in other patients in the hospital system.

Glucommander® is a product of Glucotec, Inc., based in Greenville, SC.

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PROCEEDINGS

Computerized Management of Tight Glycemic Control: "The challenge to imitate a healthy pancreas"

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Key points

- A primary unresolved issue in critical care is a methodology to reach and maintain blood glucose control safely.
- Most paper-based glucose-control protocols rely on bedside calculations using linear mathematics, whereby lowering the mean blood glucose increases the incidence of hypoglycemia.
- Since higher glucose levels are associated with increased insulin clearance, an insulin dose is not linearly related to blood glucose level.
- A computerized system using a nonlinear, physiologic insulin dosing function more closely aligns glucose control with the behavior of the human pancreas and optimizes patient outcomes with minimal hypoglycemia.
- The database generated by a computerized system also provides previously unavailable information to help clinicians assess and treat critically ill patients with hyperglycemia.

Glycemic control has value in clinical medicine because it can reduce the cost of care, shorten length of stay, improve healing, reduce nosocomial infections and reduce acute renal failure. A primary unresolved issue is a practical method to reach and maintain glycemic control safely. Current standards of care to achieve blood glucose control in critically ill patients include use of point-of-care devices to measure the blood glucose level, bedside mathematical dose calculation and intravenous (IV) insulin. This article compares bedside mathematical dose calculation with computerized management of glucose control and reviews concepts of engineering-type control mathematics applied to the complex problem of controlling elevated blood glucose levels.

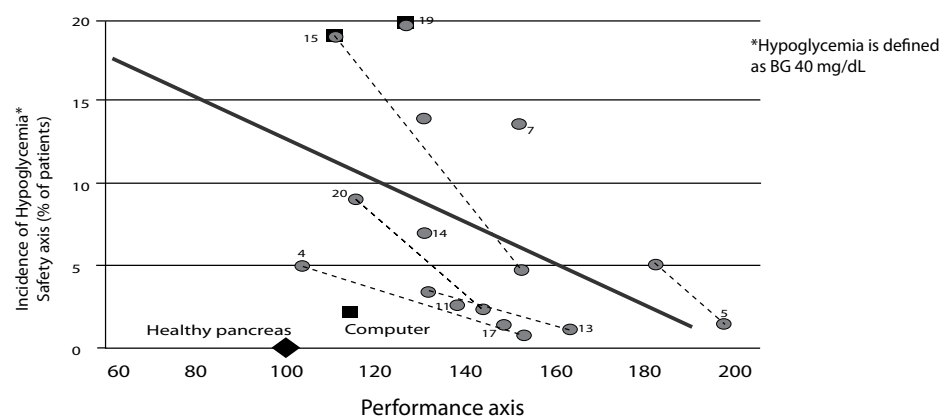
Protocols

The vast majority of paper protocols rely on bedside calculation to make dosing adjustments based on a linear IV insulin-

dosing relationship. There are thousands of variations in how hospitals and physicians expect caregivers to perform these calculations. Figure 1 illustrates a type of risk-benefit analysis that compares the performance of a number of published bedside protocols by plotting the mean blood glucose (benefit) to the incidence of hypoglycemia (risk). The dashed lines in this figure connect the control and study cohorts from these reported retrospective or randomized studies. The protocols usually use linear mathematics to determine insulin dosing and have the same characteristic: lowering the mean blood glucose increases the incidence of hypoglycemia, although most studies claim no ill effects from the observed hypoglycemia. The notable exception is the large 2006 Van den Berghe study, in which hypoglycemia was reported as an independent predictor of death.

Figure 1. Mean Blood Glucose of Study (mg/dL)

(mean of all blood glucose readings on IV insulin)



Hypoglycemia is a concern in the majority of the reported protocols for insulin infusion dosing. None of these protocols achieve the same results as the human pancreas, which regulates blood glucose without incidence of severe hypoglycemia. The protocols shown in Figure 1 are simple two-point control systems that use the current and last blood glucose levels in a linear relationship to calculate the next IV insulin dose. It would seem relatively intuitive that the benefits of tight glucose control could be offset by the side-effects of hypoglycemia. Control of blood glucose should therefore have minimal hypoglycemia as one of the primary goals.

Computerizing Insulin Dose Calculations

Compared to paper protocols, there are many advantages to the use of a computerized protocol: reduced errors, improved protocol consistency, improved compliance and discipline, a database for audits, quality assurance and improvement and a platform for subcutaneous conversion. Another advantage of a computerized insulin-dosing system is enabling the use of sophisticated mathematics that typically is not available at the bedside. Basing dose calculations on a physiologic insulin-dosing relationship is one such example. Insulin clearance is a function of the glomerular filtration rate, which, in turn, is related partially to the blood glucose level. Higher glucose levels are associated with increased insulin clearance; thus, the insulin dose is not linearly related to the blood glucose level. The use of a nonlinear, physiologic insulin dosing function should lead to improved glycemic control.

Another example of the use of sophisticated mathematics to improve glycemic control is the application of control mathematics. Control mathematics is a scientific discipline that originated in the field of engineering and has evolved to become a specialty of computer science. Millions of people rely on

control circuits every day, from thermostats and cruise controllers to the auto-pilots that guide passenger planes across the continent. The task of controlling an insulin infusion to regulate elevated blood glucose, which strongly influences patient outcomes, is left to the bedside determination of a healthcare provider.

By applying a computerized, control-mathematics approach, more than two dose/response data points can be used to precisely estimate the next dose of IV insulin. This type of calculation would be very difficult to perform at the bedside. Applying higher-level mathematics to the regulation of the insulin dosing is likely to significantly improve glucose control outcomes and result in the maintenance of normal blood glucose. The application of this type of complex mathematics is only possible with a computer. This sophisticated approach is now only available in one FDA-approved proprietary software product called the EndoTool® Glucose Management System.

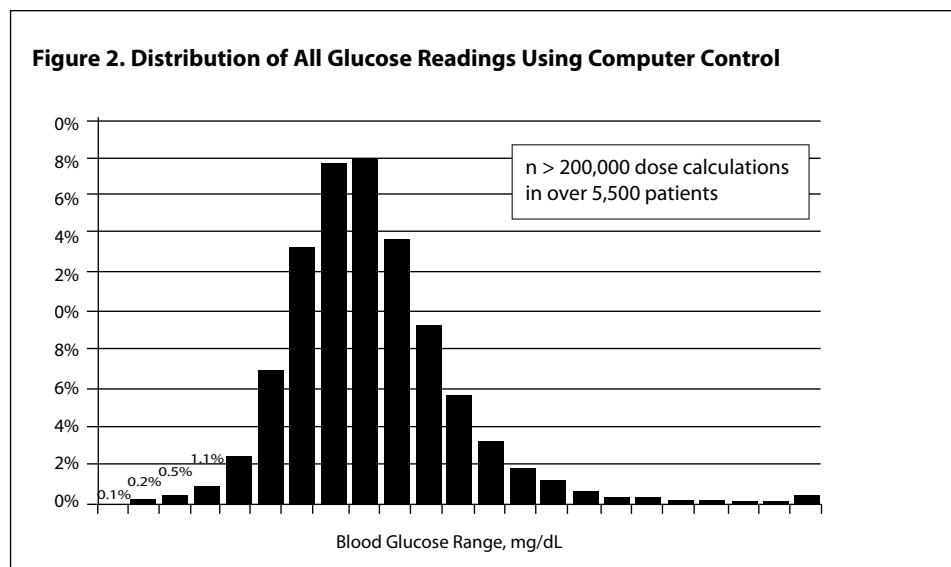
Evidenced-based Medicine

A few studies have compared the bedside mathematics approach to the computerized, control mathematics-based protocol for glycemic control. Saagar¹ randomly assigned 40

patients with diabetes scheduled for CABG and receiving D10W at 1 mL/kg/hr to either a paper protocol or to a computerized protocol (EndoTool®). In this small study the computerized method led to better control with a highly significant correlation both in the operating room ($p = 0.001$) and in the recovery room ($p < 0.0001$) without severe hypoglycemia (< 40 mg/dL). Several other studies^{2,3} that used retrospective control data have shown that the application of computer technology can reduce errors and provide more consistent dosing of IV insulin.

Results

When the mathematical approach used by EndoTool® is applied to glycemic control in critical care, glucose control is much more aligned with the behavior of the human pancreas (Figure 1). This software protocol has been the standard of care at one major hospital for more than four years³. The distribution of all of their blood glucose results is illustrated in Figure 2. The incidence of severe hypoglycemia is less than 1 per 1000 readings, with more than 60% of these low readings associated with either blood glucose determination more than 30 minutes late or when no insulin was being infused during the previous period.



Discussion

The potential for a computerized approach to improve glycemic control should be intuitive given the potential for errors and the complexity of some paper-based glycemic control protocols. Critical care nurses are overwhelmed by new protocols that have to be integrated into the care plans. Removing the need for bedside calculations by using a computerized system that reduces the workload for the caregiver should be a component of computerized glycemic control programs. Controlling the blood glucose level promptly can help reduce the frequency of point-of-care determinations and associated costs, and can lead to control similar to that achieved by the human pancreas, optimizing patient outcomes and reducing the caregiver's workload. Available alarms and quality assurance reports can improve compliance with the glycemic-control protocol.

Conclusions

The control of elevated blood glucose levels in critically ill patients is a complex problem. The use of IV insulin is ideal for glycemic control because of its short half-life. Computerized calculation of IV insulin dosing for glycemic control may be a methodology that can:

- Imitate the human pancreas' control of glucose
- Optimize patient outcomes with minimal hypoglycemia.

Computerized management of elevated blood glucose in critically ill patients can reduce human errors and improve work flow. A database generated by this method also has the potential to enhance patient care by documenting previously unavailable information to help clinicians in the assessment and treatment of critically ill patients with hyperglycemia.

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Analysis of Variation in Insulin Protocols

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Key points

- Existing insulin infusion protocols vary greatly in the details of implementation and can result in great variations in insulin dose recommendations.
- Protocols developed with one group of patients may require validation when used for other patients, but ease of use and efficacy in patients are important features of any protocol.
- A trial using a protocol may be necessary in deciding which one to use.
- Insulin protocol innovations include the use of nomograms, pre-printed tables and internet-based or computer-based protocols with automatic dose calculations.
- Involving and empowering nursing staff is critical for the success of any protocol.
- Different protocols may be required for different patients in the same hospital because one protocol may not fit all.

Protocol Development

Managing critically ill patients has dramatically changed over the past decade. Many large clinical trials have identified optimal approaches or therapies in areas where there was once a high degree of variation. There are now established protocols that have become part of the routine care of critically ill patients. Protocols reduce variation in care and promote the best available therapeutics or best practices¹. Adherence to these protocols should improve patient care and patient outcomes². Protocols are intended to complement care, however, and are not a substitute for sound clinical judgment.

Protocols are not a "cookbook" approach to patient care. Protocols may not necessarily translate well from the research setting to general patient use. Blind adoption of proto-

cols developed for other patients may compromise patient comfort or safety. Protocols require flexibility and adaptation for successful application in any patient population. Successful implementation requires a critical mass of organizational and administrative support, especially for protocols that require acceptance and use by several healthcare providers.

Examples of widely accepted protocols used in intensive care units (ICU) include ventilator management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), weaning patients from ventilators, sedation, analgesia, transfusions and more recently antimicrobial stewardship^{1,3}. Intensive insulin therapy (IIT) to control hyperglycemia in critically ill patients is another area of great interest. Adverse outcomes associated with

hyperglycemia and the merits of tight glucose control (TGC) defined as serum glucose between 80-110 mg/dL have been well documented⁴⁻⁸. Universal acceptance of guidelines for TGC is tempered by limited scientific support that remains confined to the experience from one medical center^{8,9}.

Many of these protocols have been incorporated into best practice models referred to as "bundles," with ventilator or sepsis bundles the most common. Greater benefit may result from the use of bundled management compared to the interventions alone. Many organizations have taken the lead in this approach, with the Institute for Healthcare Improvement (IHI) conducting one of the most visible campaigns advocating ventilator and central line bundles. Severe sepsis guidelines have also garnered much attention. The first guidelines arose from collaboration between the Society of Critical Care Medicine, European Society of Intensive Care Medicine and International Sepsis Forum, who collaborated on the "Surviving Sepsis" campaign¹⁰ with subsequent support from IHI. Although questions have been raised about the objectivity of the recommendations, the guidelines are highly visible within the medical community¹¹. The sepsis bundle includes recommendations for adequate glycemic control defined as a serum glucose < 150 mg/dL achieved by administering continuous infusions of insulin and glucose. The group acknowledged the limited scientific support for this recommendation. Others have been

more circumspect with their endorsement of intravenous (IV) insulin infusions and treatment of hyperglycemia¹². Nevertheless, insulin infusion protocols have become common.

Insulin Infusion Protocols

We surveyed a convenience sample of surrounding institutions and found that all had insulin infusion protocols. The protocols varied, ranging from the use of published protocols, to slightly modified protocols, to others entirely unique to the institution. The number of protocols and differences between protocols is significant. The task of identifying the most appropriate protocol can be a challenge for those trying to implement a protocol in their own institution. A protocol may be successful in one institution, but there is no guarantee of its efficacy when used in another hospital with different nursing staff and a different patient population. It is impractical to pilot test every available protocol and developing a new protocol may be time-consuming.

The diversity found in our survey of local hospitals prompted a more detailed review of published protocols¹³. The analysis started with a search of published protocols using the PUBMED search engine and the terms "intravenous insulin" and "insulin protocols." The focus was on protocols used for critically ill patients. Glucose-insulin-potassium (GIK) protocols, although similar, were not included, since the basis of these protocols was not glucose control but a reduction in free fatty acids and involved a different group of patients. The focus was on paper-based protocols, given their wide availability and ease of use. Computerized protocols were not reviewed given limited access to the programs.

Based on a review of protocols identified it became clear that some protocols had many versions. In these instances, the latest published protocol was used for review and analysis. The review focused on twelve insulin

infusion protocols, selected from 24 protocols. Significant variation was noted among these protocols in all aspects of protocol implementation, beginning with the initial insulin dose, subsequent dosing adjustments to other logistical matters.

Major Areas of Variation

Major areas of variation are summarized in Table 1. Notable differences included the threshold for initiating an insulin infusion, the initial use of bolus insulin and subsequent doses of bolus insulin. Bolus insulin treatment resulted in larger doses administered earlier in the course of an insulin protocol. Subsequent adjustments to the insulin rate were based on a variety of factors, including the direction and rate of change in serum glucose, insulin resistance with the actual change either fixed or calculated based on the actual glucose value or the insulin infu-

sion rate. While most changes to the insulin infusion rate are fixed, some protocols require adjustment using a multiplier. These adjustments may or may not require mathematical calculations with each change in the insulin dose. The target goal glucose was within the 80-180 mg/dL range; some advocating an 80-110 mg/dL goal, and others with a range of 120-180 mg/dL. Variations in the protocols are further outlined in Table 2 from Wilson, et al¹³.

While most of the protocols were nurse-driven with limited physician input, van den Berghe reported active physician guidance¹⁴. All except the Furnary protocol required a continuous glucose source, parenteral or enteral, during continuous insulin infusion¹⁵. Adjustments to hypoglycemic episodes also varied with differences in the magnitude of adjustment as the patient approached hypo-

Table 1. Areas of Variation in Insulin Infusion Protocols

INSULIN INFUSION RATE

- Presence or absence of pre-existing diabetes
- Initial hyperglycemic threshold (> 150-200 mg/dL)
- Initial bolus insulin dose (calculated [formula] versus fixed [pre-determined])
- Subsequent bolus insulin
 - Some with larger doses earlier in the protocol
- Changed in insulin dose (calculated vs fixed dose)
 - Based on direction of change in glucose (decrease, no change, increase)
 - Velocity of change (30-50 mg/dL/hr)
 - Dose adjustment for insulin resistance
 - Basis of change in insulin dose (rate, infusion)
 - Unit of change in insulin dose (fixed dose or calculated using a multiplier)
- Number of steps required (1-3); some requiring calculations to change the dose (8 of 12)
- Target glucose (80 – 180 mg/dL; with a wide range of acceptable values)

LOGISTICS OF IMPLEMENTATION

- Nurse-driven, with varying physician input
 - Adherence to protocol or allowance for changes in protocol ("protocol violations")
- Differences in frequency of glucose monitoring
- Differences in requirement of a constant glucose source (parenteral or enteral infusions)
- Adjustments for hypoglycemia (variable levels of adjustment after hypoglycemia)
- Time to goal (variable; from 2-24 hours)
- Duration within goal (not consistently reported)

glycemia and variable adjustments to the insulin rate when it was restarted. Time to goal and duration of time in the goal range were variably reported, ranging from 2-24 hours to goal and duration in the goal range in the 40-60% range.

The variation between protocols would predictably produce different recommendations and results. While comparison of the details of the protocols was possible, comparison of the performance of the different protocols was impossible. Therefore, comparison of protocols was made using a computer simulation using the results from an actual patient treated with the van den Berghe protocol. The key assumption of the simulation was that the changes in glucose occurred as a result of the insulin dose recommendations of the protocol being evaluated. The limitations of such a simulation exercise are well acknowledged, since the actual changes in glucose would differ with each protocol. This approach does however provide insight into the differences among the protocols and their recommended

insulin rates doses. In one protocol, a patient received almost 100 units of insulin before reaching the target of 80-110 mg/dL. Almost 60% of the insulin was infused after a serum glucose of 200 mg/dL with 15 units/hour the highest infusion rate. Among the other protocols, the recommended doses of insulin varied widely, ranging from a total of 27-115 units, and from 4-21 units/hr.

No Single Approach

It is clear that no single approach or protocol can anticipate and accommodate the great variety of critically ill patients. Serum glucose levels are affected by a host of influences, including infection, renal insufficiency, catabolic stress and erratic nutrition that lead to dynamic and fluctuating insulin requirements that would probably be best addressed by frequent glucose monitoring and a continuous insulin infusion. The increasing use of IV insulin infusions for glucose control has led to recommendations by the American College of Endocrinology

and American Diabetes Association^{16,17}. They outlined necessary requirements for inpatient management, including administrative support, multi-disciplinary committees, with analysis of current practices and barriers to implementation. Key components included standardized order sets or algorithms and appropriate metrics to evaluate the impact of their programs. They felt the best insulin protocols would include consideration of current and previous glucose levels, adjustments of the rate of glucose change, and the current insulin infusion rate. Recognition and adjustment for hypoglycemia was also crucial, and each protocol in use would require validation and an ongoing assessment of efficacy and safety. IIT also requires more nursing time, another consideration when choosing a protocol, since time spent on the protocol, whether in monitoring or calculating changes in the infusion rate, eventually affects other patient care areas. The index patient described had 20 glucose determinations during the initial portion of his infusion,

Table 2. Areas of Variation in Insulin Infusion Protocols¹³

Author	Target glucose (mg/mL)	Bolus insulin		Changes insulin infusion based on damages in glucose			Basis of changes in insulin rate		Steps for insulin adjustment	Time to goal glucose
		Initial	Add	Direction	Velocity	Resistance	R or I	U±%	n/calculations Y/N	
Bode	100-150	Y*	N	N	Y	Y	R	U	3/N	NR
Boord	120-180	N	N	N	N	N	R	U	1/Y	NR
Chant	90-144	N	Y	Y	Y	N	R	U+%	2/Y	15h
Davidson	< 100	N	N	N	N	Y	R	Multiplier	3/Y	7.5-10.5h
Fumary	100-150	Y	Y	Y	Y	Y	R	U+%	2/Y	NR
Goldberg	100-139	Y	N	Y	Y	N	R+1	U+%	3/Y	9.0h
Kanji	80-110	N	N	Y	Y	Y	R	U+%	2/Y	11.3±7.9h
Krinsky	< 140	N	N	N	N	N	R	U	1/N	NR
Marks	120-180	N	N	N	N	N	R	U	1/N	NR
Van den Berghe	80-110	N	N	N	Y	N	R	U+%	2/Y	12-24h
Watts	120-180	N	Y	N	N	N	R	U	1/N	8h
Zimmerman	101-150	Y	Y	N	N	N	R+1	U+%	2/Y	2.1h

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which would translate into 100 minutes spent on glucose management alone, allotting five minutes for each glucose check.

Summary

Existing insulin infusion protocols vary greatly in the details of implementation. The differences in protocols can result in great variations in insulin dose recommendations. Protocols developed with one group of patients may require validation when applied to other patients. The ease of use and efficacy in patients are important features of each protocol. A fair assessment of a protocol may not be possible without a treatment trial. New innovations are emerging, including the use of nomograms, pre-printed tables, internet-based or computer-based protocols with automatic dose calculations. Irrespective of the protocol chosen, involving and empowering nursing staff is critical for its success. There may not be one protocol suitable for all patients, and different protocols may be required for different patients in the same hospital. One protocol may not fit all.

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Improving ICU Quality and Safety: Implications for Tight Glycemic Control

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Key points

- *Structured approaches to improve the reliability of care and teamwork climate in intensive care units (ICUs) have improved patient safety and outcomes.*
- *The link between teamwork climate and tight glucose control (TGC) has not been investigated; however, TGC is clearly a team effort.*
- *Lessons learned from quality and safety research to improve infection control and post-surgical care may well be applicable to TGC.*

The Johns Hopkins Quality and Safety Research Group (QSRG), which manages several large collaboratives including more than 250 intensive care units (ICUs), has a strong focus on quality and safety issues. Studies in these ICUs have shown that a culture of safety, particularly a teamwork climate, is a predictor for many clinically important outcomes. Fortunately, teamwork and the safety climate can be improved.

The link between teamwork climate and tight glycemic control (TGC) has not been investigated but TGC clearly requires teamwork. In this article the Johns Hopkins model for improving the reliability of care, the four critical components of all change efforts, and the Johns Hopkins Comprehensive Unit-based Safety Program (CUSP) are discussed.

Improving Reliability of Care

The Johns Hopkins QSRG model for improving the reliability of care that has been developed over the past five years is based on literature showing that patients receive evidence-based therapies they should receive

only about 50% of the time¹. To improve reliability of care:²

- Pick a clinically important area—something commonly seen in the ICU or associated with significant morbidity and mortality.
- Identify “What should we do?”—what evidenced-based therapies should be provided for patients?
- Measure performance—translate those therapies into behaviors that can be measured validly and feasibly with data collected concurrently at the bedside and analyze whether those behaviors are being done.
- Focus on improving the systems of care (decreasing complexity, creating redundancy and learning from mistakes) to improve performance.
- Evaluate whether improvement in measures has been achieved.

Many individual hospitals have used this model and seen reductions in complications

and mortality and improvements in patient satisfaction, rates of nosocomial infections, glucose control and sepsis care.

For example, this model has been used to reduce catheter-related bloodstream infections (CR-BSIs), a completely preventable complication that currently results in one to eleven patient deaths every day. Studies show that CR-BSIs can be reduced by the following steps, ensuring that patients receive five evidence-based interventions as described in Center for Disease Control (CDC) guidelines³:

- Apply five best practices
 - Remove unnecessary lines
 - Perform hand hygiene
 - Use maximal barrier precautions
 - Use chlorhexidine for skin antisepsis
 - Avoid femoral lines
- Decrease complexity, e.g., create a “line cart” that has all the necessary supplies, so that providers do not have to go to eight different places to gather their supplies.
- Create redundancy, e.g., create a checklist to be completed by the nurse at the bedside and then empower the nurses to stop the procedure if a violation is noted.

Use of this model reduced the rate of CR-BSIs in the Johns Hopkins ICU from about the 50th percentile, the National Nosocomial Infection Surveillance benchmark, to less than one per thousand catheter days. Because

safety efforts focused on systems change, this dramatic reduction has been maintained in an academic medical center for the past three years. This approach can be broadly generalized. In Michigan, for example, within three months of implementing all the above interventions in 136 ICUs across the state, the median rate of CR-BSIs went to zero⁴.

Technical and Adaptive Components of Change

One of the most important lessons from our experience and the literature is the four critical components for all change efforts.

- **Engage.** Providers and front-line staff need to be engaged. More than just providing data back to providers, what can we do to touch their hearts or create that imperative for change? Telling stories is one example. Many hospitals identify patients who had adverse events and then feed those stories back to staff.
- **Educate.** Provide relevant educational material. Many providers are not able, interested or willing to read a 72-page CDC guideline on the prevention of CR-BSIs, so distill the information down into discreet behaviors known to be important. The biggest gap between current performance and best evidence is not that providers disagree with the evidence, but that they do not know the evidence exists.
- **Execute.** Provide templates or examples of how to create redundancy or standardized care within the ICU. Many of ICU teams want examples they can adapt to their local environment.
- **Evaluate.** Provide valid tools to evaluate whether care has improved.

Context of Care

Teamwork is a critically important element in the culture of safety. An aviation industry study showed that most commercial aviation

accidents happened on the first day a flight crew worked together. In healthcare, there is little training on teamwork. In labor and delivery, intensive care units and the operating room, survey data show that physicians uniformly overrate communication and collaboration compared to nurses⁵.

A highly validated safety culture assessment instrument is the safety attitude questionnaire (SAQ)⁶. The SAQ evaluates a variety of domains within the ICU—job satisfaction, teamwork climate, safety climate, perceptions of management, stress recognition and working conditions—as perceived by front-line nurses, physicians, respiratory therapists, pharmacists, aides, secretaries and other staff.

The SAQ definition of teamwork is “the perceived quality of collaboration between personnel in this unit.” Examples include “Disagreements in the ICU are appropriately resolved (i.e., not who is right, but what is best for the patient)” and “Our doctors and nurses work together as a well coordinated team.” Safety climate is defined as “perceptions of strong or proactive commitment to patient safety in this unit,” e.g., “I would feel safe being treated in this ICU” and “Medical errors are handled appropriately in this ICU⁶.”

Baseline SAQ results from Michigan ranged from an ICU in which only 15% of staff agreed they have good teamwork to another ICU in which almost 90% agreed². When survey results were correlated with subsequent efforts to reduce CR-BSIs rates, the results were striking. Of ICUs in the lowest tercile in teamwork climate, 21% went five months or more without a CR-BSI, compared to 44% in the highest-tercile ICUs. The strongest predictor of an ICU’s ability to reduce its CR-BSI rate was the answer to a single question: “Do caregivers feel comfortable speaking up if they perceive a problem with patient care?”² Perhaps not surprising when we consider that

evaluation of sentinel events and root cause analyses have shown that in the vast majority of instances, somebody knew something was not comfortable speaking up, or they spoke up and their concerns were not acknowledged.

Teamwork also is a predictor for other clinically important outcomes such as wrong-site surgeries, decubitus ulcers, delays in starting in the operating room, bloodstream infections, post-operative sepsis, post-operative infections, post-operative bleeding, pulmonary embolism/deep vein thrombosis, ventilator-associated pneumonia, nursing turnover and absenteeism⁵. The link between safety or teamwork and tight glucose control has not been investigated; however, TGC is clearly a team effort.

CUSP

Another important lesson from our collaborative efforts is that teamwork and a safety climate can be improved, as shown by results achieved by CUSP⁷. Data from the general surgical ICU (SICU) and the Weinberg oncology ICU (WICU) at Johns Hopkins showed dramatic improvements in the culture of safety. The SICU improved from one-third to 70% of respondents reporting a good safety culture pre- and post-CUSP, and the WICU improved from one-third to almost 90% (Figure). In Michigan, after two years there has been an incremental improvement of approximately 2% to 10% in teamwork and safety culture in ICUs (Figure)². Culture change takes time.

To track changes in SAQ results over time, hospitals are classified as ‘needs improvement’ if less than 60% of the providers say that they have a good teamwork or safety culture. From 2004 to 2006 CUSP implementation decreased the percent of ICUs across Michigan that “need improvement” from 84% to 41% for safety climate and from 82% to 47% for teamwork climate.

The CUSP iterative process includes the following steps⁷:

1. Evaluate culture of safety
2. Educate staff on science of safety
3. Identify defects
4. Assign executive to adopt unit
5. Learn from one defect per month and implement teamwork tools
6. Re-evaluate culture

Another important lesson learned is that there may be at least a fourfold over-reporting of teamwork and safety culture by senior executives compared to front-line staff. One approach is to have a senior executive “adopt an ICU⁸.” The executive comes to that ICU, meets with the staff, perhaps to focus on some of the safety defects and learns to better understand the clinical improvement processes and what can senior executives do to help improve teamwork, safety and culture to try to fix defects.

Another important step is to learn from defects and implement teamwork tools to prevent identified mistakes from happening again.

Teamwork tools. One teamwork improvement tool is the implementation of daily goals⁹. Setting daily goals is a powerful tool to improve communication and teamwork used in hundreds of ICUs. Another tool is morning briefings¹⁰. Before starting rounds in the ICU, the ICU physician meets with the charge nurse to ask three questions:

- Was there anything that happened last night that I need to know about?
- Are there any flow issues within the ICU, admissions or discharges you’re concerned about, i.e., where should I start rounds?
- Are there any anticipated problems today? Staffing issues are commonly identified as a problem area.

Providing an opportunity to create structured communication between the ICU attending physician and the charge nurse can lead to valuable improvements with regard to staffing teamwork and communication.

Another tool is shadowing another person in the ICU. A physician might shadow a respiratory therapist or a nurse. Medical students can shadow physicians on rounds to observe how effectively they communicate with bedside nurses, residents, other attending physicians and providers. Their observations can change the way physicians communicate.

A culture check-up tool is a structured approach to assessing improvement in safety culture¹¹. Results can be fed back to and be used by teams so they can focus on a specific question in the culture survey and develop strategies to improve that. The team check-up tool adds science to quality improvement by identifying explicit barriers and successful strategies. Teams can use this tool to discuss these barriers and improvement strategies with senior executives.

Leadership support is critically important for quality improvement. However, there is a difference between a senior executive saying,

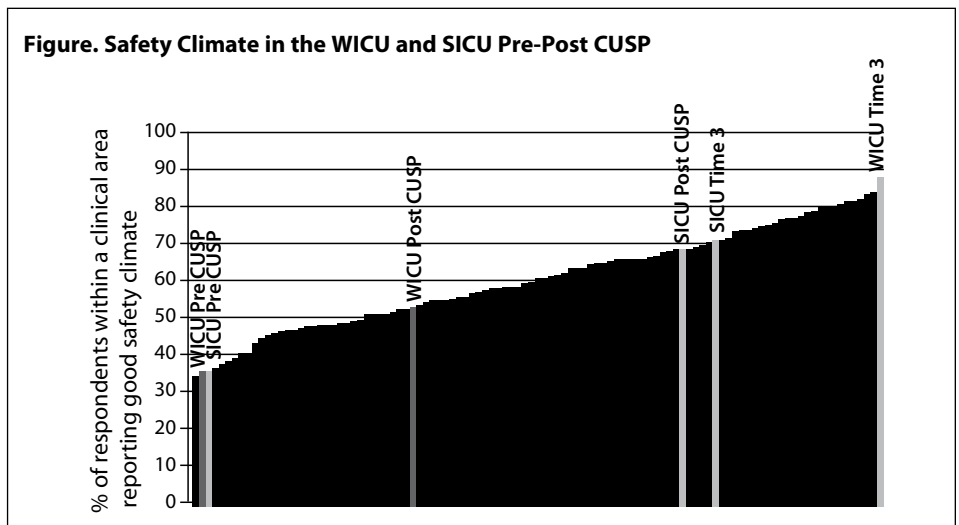
“I support you” compared with “I’m there for you three times a week or two times a week.” Leadership needs to be engaged.

Learning from mistakes by asking key questions is also a critical component of CUSP¹⁰. What happened? Why? What will you do to reduce probability that it will happen again? How do you know risk is reduced?

Finally, we have been working with teams to develop strategies to track progress in improving patient safety. A safety scorecard can be developed to track safety and teamwork on measures such as the number of BSI/1000 patient days, percent of patients receiving the ventilator bundle of evidence-based practices, percent of months in which a unit learned from a defect, the number of units in which 60% of staff report positive teamwork and safety climate and average score in each ICU. The scorecard, including safety and teamwork findings, can help feed results back to staff and increase awareness of safety throughout the organization, including senior leadership^{12,13}.

Summary

Front-line staff and senior leadership need to view safety as a science and focus on



Safety climate in surgical ICU (SICU) and Weinberg ICU (WICU) at The Johns Hopkins Hospital over time and pre- and post- implementation of the Comprehensive Unit-based Safety Program (CUSP). Each yellow bar represents the percent of providers in an individual ICU, clinical area or ward that reported a good safety climate on the Safety Attitudes Questionnaire (SAQ).

systems to ensure patients receive the therapies they should. Both the technical and the adaptive components of change must be addressed. Culture trumps strategy, and efficient, structured approaches must be used to learn from mistakes and improve safety culture. Efforts to improve glucose control within the ICU would be remiss if they do not explicitly address culture and the prior beliefs of the ICU staff. Fortunately, tools such as CUSP can now be used to help improve culture. The ultimate goal is to help teams be able to say that a patient is less likely to be harmed this year as opposed to last.

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Specialized Nutrition Support and Glycemic Control

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Key points

- *Hyperglycemia associated with specialized nutrition support (SNS) may compromise intended treatment goals. Thus, clinicians need to consider physiologic glycemic management as a primary goal.*
- *A new approach is to:*
 - *Provide SNS to all patients based on nutrition assessment and severity of illness, with glycemic control given priority over provision of adequate energy.*
 - *After glycemic control is achieved, usually in 24 to 48 hours, advance nutrition while maintaining glycemic control.*
 - *The Nutrition and Metabolic Support Service at Sharp Memorial Hospital has observed that this approach minimizes hyperglycemia for patients receiving both parenteral and enteral nutrition.*
 - *For patients who are eating, a “glycemic control diet”—which provides controlled calories, adequate protein and the same carbohydrate with each meal—allows more predictable prandial insulin dosing, compared to the conventional 1800-2000 calorie diet, is well accepted by patients and leads to better prandial glycemic control.*

The benefits of tight glycemic control (TGC) are being embraced for the care of critical and acute care patients. Successful glycemic management is integrally related to the nutrition provided to a hospitalized patient. A new look should be taken at hospital nutrition with physiologic glycemic management as a primary goal. The glycemic effects of specialized nutrition support (SNS) for hospitalized patients (parenteral [PN] and/or enteral nutrition [EN]) have been examined more than the effects of oral diets, and lessons learned from the glycemic effects of SNS should be applied to patients taking oral diets. Based on the currently available data,

a reasonable approach regarding hospital nutrition is to provide nutrition in a manner that fosters glycemic control as first priority and achieves “goal” calories as a secondary priority. This prioritized approach is increasingly used with SNS and should be applied to all hospital nutrition, including oral diets.

Nutrition Goals and Fears

Nutrition goals for hospitalized patients include the provision of essential nutrients to maintain energy, metabolic homeostasis, organ function and functional capacity. There are several concerns about the current recommendations for the nutrition care

of hospitalized patients. One of these concerns is the possibility that inadequate calorie intake will accelerate malnutrition because of the “hypermetabolism” of illness and the nutrient needs of patients will be unmet during illness. Most illnesses do not accelerate total energy expenditure significantly and short-term underfeeding is well tolerated by most non-critically ill patients¹.

In contrast, the harm from overfeeding is now well recognized. The benefit of meeting metabolic needs at the expense of creating hyperglycemia is doubtful at best and harmful at worst. From the Leuven studies², it is clear that in critically ill patients, providing SNS while permitting hyperglycemia results in worse outcomes than maintaining euglycemia (Figure)³. No comparable study is available in patients who are not dependant on SNS, but the harmful effects of hyperglycemia related to diet appear clear (Table 1). Hyperglycemia during feeding results in catabolism, is immunosuppressive and proinflammatory, and delays gastric emptying. Postprandial hyperglycemia is recognized as a major element in the long-term complications of diabetes. Based on these observations, nutrition-related hyperglycemia appears to be counterproductive to the basic goals of hospital nutrition.

Another concern about hospital nutrition which affects feeding recommendations is that hospital feeding reverses the catabolic effects of illness. A large body of evidence indicates that no single or combination of

macronutrients prevents illness-related catabolism⁴. This is not to say that prolonged starvation in illness is desirable or can be tolerated indefinitely⁵. Feeding that induces

hospital setting⁷. The American Diabetes Association position statement regarding medical nutrition therapy make 63 recommendations⁸. Approximately 50% of these

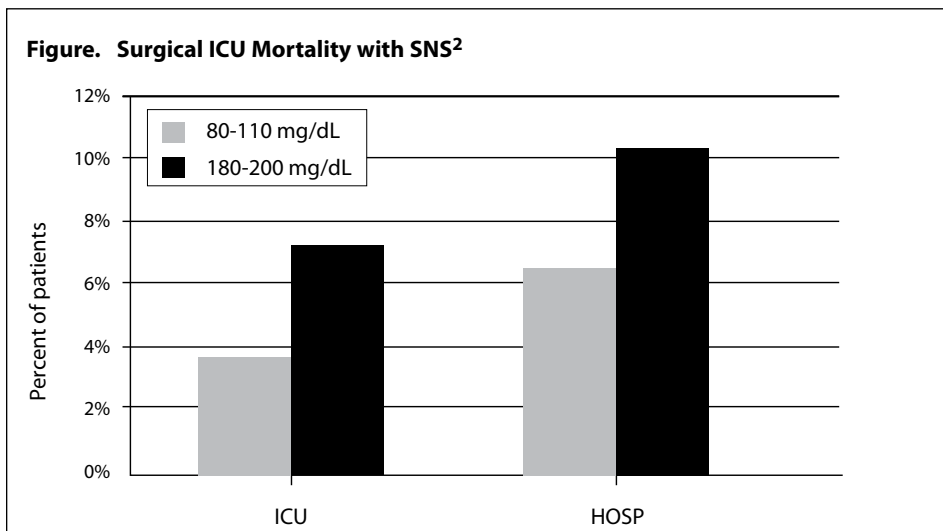
grams of glucose (references)—the equivalent the carbohydrate (CHO) contained in about five cans of common soft drinks.

When viewed in this perspective, such recommendations are counter-intuitive and not what would be recommended even for healthy individuals. Two hundred grams of clear-liquid CHO will induce hyperglycemia, especially if prescribed without regard to weight. Typically, a patient with a body mass index (BMI) of 30 consumes about 250 grams CHO with mixed glycemic index⁹, much lower than the glycemic index of 200 grams CHO in clear-liquid diet. Giving 200 grams clear-liquid CHO to newly hospitalized patients, often with poorly known insulin sensitivity and often irregular intake, makes prandial insulin administration difficult. As a result, it is overly simplistic to just recommend “adequate insulin” to control the glycemic excursion related to meals.

Glycemic Control and Nutrition: A New Approach

A rational approach to nutrition for hospitalized patients that avoids hospital-related malnutrition is to base nutrition intake on the degree of malnutrition and severity of illness. Such an approach permits under-feeding, when it is safe, and ensures that adequate nutrition is provided during prolonged hospitalization and severe illness.

Our Nutrition and Metabolic Support Service has used this approach to SNS. We have minimized hyperglycemia both in patients receiving PN and EN⁵. We stabilize glycemic control first, then start with EN when the blood glucose level is < 200 mg/dL or PN at < 15 cal/kg/day, and advance to measuring resting energy expenditure [REE] or synchronously estimating increasing insulin doses as needed. For patients who are eating, we have developed a “glycemic control diet” (Table 2), which provides controlled calories, adequate protein and the same CHO with each meal, to allow more predictable prandial insulin



Adapted from Van den Berghe, et al. *New Engl J Med* 2001;345:1359-67.

hyperglycemia adds to the catabolic effects of illness, rather than achieving the desired anabolic effect.

Current Recommendations

The question is whether we first meet estimated nutrition needs at the expense of hyperglycemia, or stabilize glycemia first and then synchronously increase energy intake and insulin as needed while maintaining glycemic control? Current recommendations stress the former based on an application of outpatient approaches to the

are Grade A-B recommendations; the others are mostly expert opinion. This strongly indicates the lack of adequate research in this area. The American Association of Clinical Endocrinologists (AACE) position statement about hospital nutrition states that adequate nutrition intake must be assured and that calories restriction is not the way to maintain glycemic control; rather, adequate insulin should be used. The sequence mentioned above, however, is not addressed in these recommendations. In fact, the recommendation is that all clear-liquid diets should contain 200

Table 1. Harmful Effects of Hyperglycemia Related to Nutrition

- Impaired protein synthesis
- Catabolic
- Immunosuppressive and proinflammatory effects
- Increased mortality and complications in the critically ill
- Delayed gastric emptying

dosing. Our unpublished observation is that this diet is well accepted by patients and leads to prandial glycemic control with fewer excursions compared to starting with the conventional diet of 1800 to 2000 calories for

Table 2. Glycemic Control Diet

- High protein ~ 70 gms
- Limited energy ~ 1200 cal/day
- Controlled carbohydrate
- High fiber
- No HS snack
- Three day mandatory RD review

all eating patients. Needless to say, we avoid glucose in clear-liquid diets; in fact, we discourage clear-liquid diets for most patients.

Summary

Nutrition should be provided to all patients based on nutrition assessment and severity of illness, with glycemic control given priority over adequate energy provision. After glycemic control is achieved, usually in 24 to 48 hours, nutrition should be advanced while maintaining glycemic control. This principle should be applied both to eating patients and to those receiving SNS.

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PROCEEDINGS

Examining Medication Errors Associated with Intravenous Insulin

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Key points

- *Insulin therapy is fraught with patient safety concerns and the potential for medication errors.*
- *USP MEDMARX® data show that:*
 - *Compared with other medication errors, intravenous (IV) insulin errors are six times more likely to result in harm.*
 - *The majority of IV insulin errors occur during administration by nurses.*
 - *The leading causes of IV insulin errors are performance deficit, procedure/protocol not followed, and communication.*
- *The following are frequent problems with IV insulin therapy:*
 - *IV pump programming errors*
 - *Confusing IV insulin with another IV piggyback*
 - *Order incorrectly entered by pharmacy*
 - *Patient tampering with IV pump*
 - *Staff unfamiliar with glucose protocol leading to inadequate monitoring, unclear control orders*
 - *Incomplete documentation*
- *Policies, procedures, or protocols for tight glycemic control should be developed with consideration of the potential for increasing the opportunities for harmful medication errors and adverse drug events.*

While the risks and benefits of intensive insulin therapy (IIT) to manage blood glucose levels continues to be debated, it is important to recognize that patient risks associated with insulin use go beyond episodes of hypo/hyperglycemia. Medication errors that can lead to adverse drug events (ADEs) are another issue that should be included in the discussion about the safety and efficacy of insulin therapy. Medication errors are preventable events that arise from the interplay

between people, processes, technology and products.

Medication errors involving insulin have been reported for many years, but despite this, their common occurrence continues¹⁻⁵. According to the most recent MEDMARX® report published by the United States Pharmacopeia (USP), insulin, in all its dosage forms, has been the most commonly reported product involved in errors overall and the leading product involved in harmful errors⁶. Analysis of these reported events by patient

safety experts has identified the following problems with insulin.

- A hand-written “U” for units being misread as a number
- The many types of insulin products (approximately 26)
- Similarity between brand/generic names and packages (e.g., Humalog Mix 75/25® and Humulin 70/30® and Novolog Mix 70/30® and Novolin 70/30®)
- Wide access to insulin as floor stock in most hospitals/health systems
- Many dosing schedules and ‘sliding-scales’ within an individual facility
- Non-standard, compounded intravenous (IV) solutions and infusion rates

USP MEDMARX® Data Findings – IV Insulin

Analysis of data submitted to USP’s MEDMARX® program during the five-year period from January 2002- December 2006 provides additional information about the severity, origin, types and causes of IV insulin errors. During this period, 1,298 IV insulin errors were reported with approximately 9.3% ($n = 121$) of these causing harm to the patient. The average percentage of harm for error reports submitted to MEDMARX® has been approximately 1.5%, indicating that an error involving an IV insulin product is six times more likely to result in harm (Categories E-I) (Table 1) compared to other medicines.

Previous studies have shown that the majority of medication errors are with either prescribing or administration of medicines^{7,8}. The majority (56%) of errors involving IV insulin originate during administration, followed

error (20.5% general errors vs. 7.4% for insulin errors), drug prepared incorrectly (4% vs. 6.2%), wrong administration technique (1.4% vs. 4.9%) and wrong route (1.5% vs. 4%). This suggests that compared with prescribing IV

Most patient safety experts agree that there are many causes for medication errors. Among the more than sixty different causes tracked in the MEDMARX[®] program, the leading causes associated with IV insulin errors were performance deficit, procedure/protocol not followed, and communication (Table 3). Performance deficit is often cited in combination with procedure/ protocol not followed, indicating a logical connection between them. Both of these leading causes were cited more often for IV insulin error events compared to the general data set (45.4% vs. 39% for performance deficit and 31.5% vs. 17.5% for procedure/protocol not followed).

Contributing factors such as distractions, inexperienced staff and workload increase are often cited in reports when performance deficit or procedure/protocol not followed are listed as error causes. This may explain, in part, their high ranking among the many possible causes that a reporter may select. Other causes reported more frequently with IV insulin errors were monitoring inadequate/lacking, calculation error and improper use of IV pumps. These findings identify areas where safety improvements are needed. Discussions on implementing new policies/procedures for tighter glycemic control should examine errors associated with failing to follow

Table 1. Severity of IV Insulin Errors

Error Category	n	%
Potential Error		
A	51	3.9
Intercepted Error		
B	277	21.3
Non-harmful Error		
C	479	36.9
D	370	28.5
Harmful Error		
E	108	8.3
F	9	0.7
H	3	0.2
I	1	0.1
Total	1,298	100

For complete definitions of the NCC MERP Error Category Index, see nccmerp.org

by 17% in dispensing, 14% in transcribing and 9% in prescribing activities. This distribution differs from that of overall errors in the general MEDMARX[®] dataset: i.e., errors originating in administering activities are approximately 31%; dispensing, 23%; and transcribing and prescribing, approximately 22%. Reflecting the medication-process stages where errors originated, nursing staff were most frequently involved with IV insulin errors (68%), followed by pharmacy staff (22%) and prescribers (9%).

The three most frequently reported types of error were wrong dose, omission and unauthorized/wrong drug, which together comprised nearly 70% of all error-type selections (Table 2). These error types are also among the leading types of error in the general MEDMARX[®] data set. There were, however, differences between the general data set and the sub-set of IV insulin errors for several other types of errors, including prescribing

insulin therapy, there are more problems with preparing IV insulin infusions, either in the pharmacy or by nursing staff, with administering the infusion (wrong administration technique), e.g., programming and using an IV pump and wrong route errors, e.g., administering long-acting insulin intravenously.

Table 2. Most Frequently Reported Types of Error Involving IV Insulin^a

Error Type	N	%
Wrong Dose	523	41.0
Omission Error	278	21.8
Unauthorized/Wrong Drug	119	9.3
Prescribing Error	94	7.4
Drug Prepared Incorrectly	79	6.2
Wrong Administration Technique	63	4.9
Wrong Time	54	4.2
Wrong Route	51	4.0
Extra Dose	42	3.3
Wrong Patient	41	3.2

USP's MEDMARX[®] program tracks 14 different types of error. Only the 10 most frequently reported involving IV insulin are shown.

policies/procedures and insufficient patient monitoring to avoid introducing new error opportunities.

Selected Insulin Error Reports

Case #1: An insulin infusion was ordered for an ICU patient. The infusion was started at the wrong rate with subsequent bolus and rate changes not administered as ordered by the physician. Fasting blood sugar was 27mg/dL, and the patient was found unresponsive and diaphoretic. Dextrose 50% IV was ordered and administered and the patient remained in the ICU for a prolonged period of time.

Case #2: An insulin infusion was ordered and started pre-operatively on a patient undergoing kidney transplant. Post-operatively, the patient was transferred to the ICU without the insulin drip. After this was discovered, it was determined the patient’s blood glucose was 443 mg/dL and significant electrolyte abnormalities. Dialysis was reinstated on the patient, who also required a lengthened ICU stay.

Case #3: A patient with diabetes in the ICU was receiving an IV infusion of regular insulin 1unit/mL at a rate of 10 units/hour titrated per sliding scale. After changing to a new bag of insulin, the IV pump was reset manually to

clear prior totals and to enter the new volume that was to be infused. Shortly after the new bag was hung, a nurse noticed that the infusion pump was incorrectly set at 150mL (i.e., 150 units) per hour. The infusion was stopped and the patient was given orange juice and closely monitored for the next three hours. If the total volume of the bag (100mL) had been infused at the rate of 150mL/hour, it would have taken only 40 minutes for the patient to receive 100 units of insulin, potentially causing irreversible brain damage and/or death from cerebral edema and insulin shock.

Common Error Scenarios

A review of several hundred reported error events identified the following frequently occurring problems:

- Incorrect infusion rates (generally by a factor of 10) as a result of incorrectly programming the IV pump (e.g., 60 units/hr vs 6 units/hr)
- Mix-ups with another IV piggyback (e.g., anesthesiologist infusing insulin thinking it was the antibiotic)
- Order incorrectly entered by pharmacy leading to incorrect concentration prepared and infused

- Patient tampering with IV pump causing an increased infusion rate
- Staff unfamiliar with glucose protocol leading to inadequate monitoring, unclear control orders
- Incomplete documentation on medication administration record leading to unclear or omitted rate information, when infusion started, etc
- General IV pump programming errors

Conclusion

Insulin therapy is fraught with safety concerns and the potential for medication errors. Data submitted to USP’s MEDMARX® program can help identify where safety risks exist and how current practices contribute to error events. Any discussion of implementing new policies, procedures or protocols for tight glycemic control should proactively evaluate their potential for increasing the opportunities for medication errors and ADEs.

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Table 3. Most Frequently Reported Causes of Error Involving IV Insulin

Cause of Error	n	%
Performance/ Human Deficit	583	45.4
Procedure / Protocol not followed	405	31.5
Communication	172	13.4
Knowledge deficit	159	12.4
Computer entry	140	10.9
Documentation	113	8.8
Monitoring inadequate / lacking	111	8.6
Calculation error	109	8.5
Pump, improper use	104	8.1
Transcription inaccurate/missing	100	7.8

USP’s MEDMARX® program tracks 67 different types of error. Only the 10 most frequently reported involving IV insulin are shown.

The Portland-Vancouver Regional Inpatient Glycemic Control Collaborative

Chris Hogness, MD, MPH, Southwest Washington Medical Center, Vancouver, WA

Key points

- *A regional focus on providing optimal inpatient care to diabetic patients is clearly needed.*
- *State collaboratives supporting chronic disease management, including diabetes, in the outpatient setting have become increasingly common over the past decade.*
- *Locally based, inpatient quality collaboratives, in which hospitals directly competing for market share agree to cooperate and transparently share their work in quality improvement, are an emerging phenomenon.*
- *In a regional inpatient glycemic control collaborative convened by Southwest Washington Medical Center (SWMC) in September 2006, participating hospitals share glucometric data to assist members in identifying and learning from best practices and to stimulate regional improvements in inpatient glycemic control.*
- *The work of a task force convened by the Society of Hospital Medicine (SHM) to develop practical recommendations for glucometrics in the hospital has been helpful.*
- *The open sharing of different approaches to inpatient glycemic control has benefited all institutions in the collaborative.*

A focus on providing optimal inpatient care to diabetic patients in our region is clearly needed. From 1994 to 2004 the percentage of adults with diabetes in Washington State increased from 4% to 6%. In 2002, diabetes-related hospitalizations in Washington State cost \$1.1 billion. One of the more important sequellae of diabetes is cardiovascular disease, which was responsible for nearly 4 out of 10 hospitalizations in Washington State in 2002¹.

State collaboratives supporting chronic disease management, including diabetes, in the outpatient setting have become increasingly common over the past decade. For example, more than 100 outpatient health-care facilities participated in the Washington

State Collaborative on Diabetes and Cardiovascular Disease from 1999 through 2005¹.

Locally based, inpatient quality collaboratives, in which hospitals directly competing for market share agree to cooperate and share their work in quality improvement, are an emerging phenomenon. In some cases this work has been coordinated by an outside intermediary (such as a state health department, academic institution, or quality improvement advocacy group), either nationally, as in the Institute for Healthcare Improvement's 100,000 Lives and 5 Million Lives Campaigns, or locally, as in the Michigan Health and Hospital Association's Keystone

Center for Patient Safety and Quality collaborative effort to reduce central-line-associated blood stream infections.

Perhaps less commonly, local or regional health care delivery organizations are directly bringing themselves together to share quality improvement work. The announcement in May 2007 that Adventist, Wellmont and Novant health systems were launching a collaborative effort to reduce medical error by "creating metrics and identifying best practices that can serve as a template for promoting patient safety at hospitals nationwide" is one example of what may become a more widespread trend².

There is much to gain and little to lose for competing hospitals to collaborate in quality improvement work. Hospitals who are furthest along in developing a particular quality improvement program may vault themselves into a position of regional quality leadership in convening a collaborative of local hospitals to share their work. Hospitals less far along the path can accelerate their progress by participating in a regional quality improvement collaborative and learning from the work of peer organizations. Ultimately the patients in the region benefit—and it is sometimes worth emphasizing that one never knows in which hospital one may be personally a patient (including those of competing organizations). This is what gives the quality improvement dictum to "steal shamelessly and share senselessly" its very rational foundation.

The Portland-Vancouver Regional Inpatient Glycemic Control Collaborative

Following a one- to two-year period of intense focus on inpatient glycemic control, Southwest Washington Medical Center (SWMC) convened a regional inpatient glycemic control collaborative initially attended by nine hospitals in the Portland-Vancouver area in September 2006. Hospital personnel who attended the first meeting included physicians (hospitalists, surgeons and endocrinologists), nurse managers, diabetic educators and pharmacists from Oregon Health and Sciences University, Kaiser Sunnyside, the Portland VA hospital, Providence Portland, Providence St. Vincent, Legacy Emanuel, Legacy Salmon Creek, Adventist and SWMC. We met in December 2006, March 2007 and June 2007, and plan to continue meeting with every three months for the foreseeable future. Over this period other hospitals from the Providence and Legacy systems joined the group. The participating health system farthest from the Portland-Vancouver metropolitan area is Asante Health Systems in Bend, Oregon.

All participating hospitals are committed to transparently sharing glucometric data for purposes of inter-hospital comparison across the region. We believe that this will assist us in identifying and learning from best practices, stimulating regional improvements in inpatient glycemic control. The work of a task force convened by the Society of Hospital Medicine (SHM) to develop practical recommendations for glucometrics in the hospital has been helpful³.

Participating hospitals came to the collaborative with a wide range of experience in inpatient glycemic control and varying degrees of initial access to glucometric data. Some, including SWMC, had already examined their hospitals' glucometrics using a

glucometer-value denominator (e.g., percent of glucometer values in different areas of the hospital within specified ranges) as opposed to a patient-denominator (e.g., percent of patient-monitored days for which all or all but one values are in a specified range). Some hospitals were in the initial stages of getting access to their data or had not yet begun to do so.

At our June 2007 meeting, we agreed on the following metrics with which to compare data:

- Patient-monitored day = a day on which a patient has at least two glucometer values recorded.
- Patient-controlled day for ward patients = a patient-monitored day in which no more than one glucometer value is outside of a range of 70-180 mg/dL.
- Patient-controlled day for intensive care unit (ICU) patients = a patient-monitored day in which no more than one glucometer value is outside of a range of 70-150 mg/dL.

In addition, for our ICU patients, many or most of who are on insulin infusions, often with hourly glucose checks, we will also compare percent of glucometer values (glucometer denominator as opposed to patient-monitored day denominator) within the range of 70-150 mg/dL. This issue is addressed well in the SHM document referenced above³.

As a collaborative, openly sharing our different approaches to inpatient glycemic control has benefited all participating institutions. SWMC has shared the process we used to develop a pharmacist/clinical diabetic educator (CDE)-centered glycemic control team with other institutions thinking of developing similar teams. We also have shared our work in educating nursing in glycemic control and in developing insulin infusions, e.g., the recently published SWMC protocol⁴. At our June meet-

ing, collaborating institutions agreed to investigate each instance of a glucose less than 40 mg/dL and to report back to the group on this process at our fall meeting. We feel that meeting at three-month intervals works well for us at this time.

We have done this work without budgeted financial support. This may be a limiting factor as the group considers taking on more structured, regional quality improvement activities. One possibility for collaboratives to obtain funding may be to approach insurance companies or other potential donors to support the development of a more well-resourced, formalized collaborative focused on assisting all hospitals in the region to achieve optimal institutional glycemic control.

National networking with benchmark institutions has also been useful to many of us in the collaborative. The range of practices reported in the SHM Workbook for Improvement on inpatient glycemic control has been helpful in this regard⁴. Other opportunities for national collaboration may emerge from a national training conference for quality improvement teams working on inpatient glycemic control hosted by SWMC and Oregon Health and Sciences University in Vancouver, Washington in October 2007. This program targets the range of people involved in inpatient glycemic control, including pharmacists, CDEs, nurses, quality improvement personnel, information systems staff, hospitalists, endocrinologists, surgeons, critical care physicians, hospital administrators and others.

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PROCEEDINGS

Building Transitions from the ICU to the Ward for the Hyperglycemic Patient: One Piece of the Puzzle

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Key points

- A rational, step-wise approach can ensure successful transitions from intravenous to subcutaneous insulin regimens.
- Some variation of this step-wise approach to transition should be developed into a standardized protocol for every institution.
- Multiple methods can enhance reliability of protocol use, including:
 - Educate staff about the protocol.
 - Design the protocol guidance into the orders used at the point of care.
 - Make the protocol the “default” method for making the transition.
 - Automate or delegate special teams to assist in the transition.
 - Measure results obtained after protocol implementation to further refine and revise the protocol.
- The Society of Hospital Medicine has a web-based “Glycemic Control Resource Room” designed to assist Glycemic Control teams with all aspects of building and effectively implementing a series of linked glycemic control/hypoglycemia prevention protocols.

Case Study

RW is a 60-year-old hyperglycemic male in the intensive care unit (ICU) with multiple medical problems. He is on full-dose, continuous tube feedings at 40 mL/hr, and he has been on intravenous (IV) insulin infusion at a stable rate of 3 units/hr over the last 6 hours. Prior to falling ill, his baseline A1c was 8.7%, and his outpatient regimen was 30 units of 70/30 mixed insulin and an oral hypoglycemic agent. The problem: maintaining good glycemic control safely as RW transitions to a general medical ward that does not support IV insulin infusion, while continuing enteral tube feeding.

Mismanagement of transitions like this may lead to prolonged hyperglycemia, hypoglycemia or, in the case of an insulin-dependent patient deprived of basal insulin, diabetic ketoacidosis (DKA). Safe and effective

transitions can be accomplished reliably with the use of a step-by-step method that we are adopting at our institution.

Step 1. Calculate the amount of insulin the patient requires over 24 hours. For example, an insulin infusion rate of 3 units/hr would lead to an insulin requirement of 72 units in 24 hours (Table 1).

Step 2. Decrease this dose to ensure a safety cushion. Just as insulin requirements increase with increasing physiologic stress and illness, insulin requirements can be reduced as the patient improves. One method to insert a safety cushion is to simply take the most recent stable-infusion rate times 20 (instead of 24). In the above example, this yields an estimate of 60 units. Note that while you have introduced a safety cushion, your estimate of insulin requirement is still twice the insulin dose RW took as an outpatient.

Step 3. Assess whether the insulin requirement was furnishing basal insulin needs, or basal and nutritional needs. In

Table 1. Step-wise Approach: Transitioning from IV to SC Insulin

- Calculate how much IV insulin the patient has been requiring. Modify down for safety cushion.
- Was this insulin supplying basal requirements, or basal and nutritional requirements? Translate into the subcutaneous regimen.
- Consider any nutritional changes that may be implemented at the time of the transition off of the drip.
- Make sure SC insulin is given before discontinuation of the IV insulin.

this case, the insulin was furnishing both basal and nutritional needs.

Step 4. Allow for nutritional changes that also may occur during the transition away from infusion insulin. Very often, a patient's nutritional intake and plan also may change at the same time you transition to subcutaneous (SC) insulin. In the case of RW, however, the patient is to continue on the same full-dose enteral tube feedings.

Step 5. Apply this knowledge to create a SQ basal-bolus insulin regimen for the patient. For this patient, 60 units represents the total daily dose (TDD) of insulin, the dose of insulin required for a patient taking in a full nutritional load. Using the 50:50 rule, half of this TDD (or 30 units) should generally be supplied in the hospital as a long-acting, peakless, basal insulin such as insulin glargine or the more recently available insulin detemir. For a patient on continuous enteral tube feeding, the remaining 30 units can be supplied in split doses of rapid-acting analogue insulin (RAA-I) (5 units q 4 hours) or, alternatively, as split doses of regular insulin (7 units q 6 hours).

Step 6. Make sure the SC insulin is given PRIOR to stopping the insulin infusion! Build this premise into your order sets and protocols.

Correction-dose regular insulin could be given along with the nutritional doses as needed.

What if RW had indicated he was ready to try an oral diet, and you wanted to discontinue enteral tube feedings at the same time you transferred him to the wards (Table 2)? Step # 4 would mandate that you take this into account. His basal insulin dose would remain the same, but his nutritional requirement estimate would be better delivered as a RAA-I in three divided doses with meals (10 units of RAA-I q AC). Patients just starting a diet are not always reliable in taking in

Table 2. Enteral to PO

- What if, instead of continuing enteral nutrition on the floor, you opt to stop enteral nutrition and start the patient on a mechanical soft diet?
- Glargine 30 units = Basal
- RAA 10 units q AC = Nutritional/Prandial
(If you expect them to eat a full meal!)
- If PO intake suspect at first, use CHO counting, or empirically reduce nutritional RAA dose and give the dose just after the meal instead of just *before* the meal.
- Correction dose RAA insulin also needed.

their full nutritional requirement, so the treatment team needs to take this into account. Solutions may include carbohydrate counting for the nutritional component, empiric reduction of the nutritional insulin requirement, or withholding the nutritional insulin dose until just after the patient eats, to allow for a better estimate of nutritional intake and the expected carbohydrate-induced glycemic excursion.

An inpatient with hyperglycemia frequently makes many transitions across several care-giving teams and locations during a single inpatient stay, and the transition from insulin infusion to a SC regimen is but one piece of the puzzle. How can we improve the reliability of care provided for patients in such a rapidly changing environment, as the patient undergoes changes in nutritional intake, insulin requirements and varied access to insulin infusion? The answer generally lies in standardizing the care and monitoring process via a series of institution-specific protocols. These protocols should be linked and reference each other in a consistent way. The insulin infusion protocol, for example, should contain a hypoglycemia protocol, standards for monitoring glucose values, guidance for transitioning the patient to SQ insulin and a direct reference to an institution-specific SC insulin regimen. The guidance from the protocols should be designed into order sets and workflow.

The Society of Hospital Medicine has built a web-based "Glycemic Control Resource Room"¹ designed to assist Glycemic Control teams with all aspects of building and effectively implementing a series of linked glycemic control/hypoglycemia prevention protocols. This invaluable resource takes a broad view of the inpatient hyperglycemia /diabetes issues and addresses everything from how to

Table 3. Performance Improvement Principles

- Obtain institutional buy-in/support.
- Form a multidisciplinary team.
- Set achievable but aggressive goals.
- Use metrics that are reliable, practical.
- Pay attention to ease of use of orders/protocols.
- Identify "best practice"; standardize choices.
- Layer interventions and methods to enhance reliability.
- Fail faster: ongoing feedback and refinement.
- Education: always necessary, but rarely sufficient if used alone.

build an effective team, to garnering institutional support and building the business case for glycemic control efforts, to enhancing reliable care via effective implementation of protocols and structured order sets. The principles of performance improvement (Table 3) are illustrated throughout with examples that apply to inpatient glycemic control issues.

“Hierarchy of Reliability”

An important concept that has emerged from this work is the “Hierarchy of Reliability,” i.e., the success in ensuring that best practice is followed is a function of how far up this hierarchy your team has gone (Table 4).

At Level 1 Reliability, there is no standardization, and achieving a reliable transition from IV to SQ insulin would depend entirely on the knowledge and vigilance of individual practitioners. At Level 2, a protocol or instructions for making the transition may exist, but they are not well integrated into the flow of work, and thus guidance remains largely unavailable for the major of patients. At Level 3, we start to see some serious improvement in reliability. Protocols exist for IV and SQ insulin. Furthermore, the guidance provided by the protocols (for calculating insulin doses, choosing regimens for different nutritional scenarios, glucose monitoring, when to call a physician, hypoglycemia care and desirable glycemic targets, etc) is available to front-line workers in the form of cues built into

the structured order sets and documentation forms. At Level 3, you can expect measurable improvement, and reliability increases to 65% to 85%.

At Level 4, a variety of other performance-improvement and high-reliability design techniques are layered onto Level III efforts including education.

Examples would include:

- Making the protocol the “default” method for making the transition.
 - For example, orders to discontinue insulin infusion would require the use of an IV to SQ insulin order set, which would lead the provider through the logical steps of the transition protocol. Providers may “opt out” of the suggested doses and regimens called for in your protocol, but they must go through your protocol steps and explicitly choose to opt out, since your protocol is the default method.
- Automation or delegation of a special team to assist in the transition.
 - Going one step further, nurses, pharmacists, or some other specially trained team would be empowered to activate and carry out the protocol, assisting the provider in making this transition in a standardized way. In institutions with

computerized, closed-loop insulin infusion protocols, autocalculation of the ideal suggested basal–bolus SC insulin regimen has been demonstrated with good effect.

- Measurement of results obtained after protocol implementation to further refine and revise the protocol, and to provide feedback to the providers.

At Level V, real-time data are used to monitor the transition process. Individual patients who do not attain an optimal transition are identified in near real-time, and remedial action occurs concurrently. Furthermore, these outliers are scrutinized carefully to further refine the protocol and the manner in which it is implemented. Reliability of over 90% can be attained at this level.

Summary

It is very common for a patient to transition from IV insulin infusion to an SQ insulin regimen. Unfortunately, this transition is often mismanaged, with resultant loss of glycemic control or avoidable hypoglycemia. Improvement teams need to devise best-practice protocols for insulin management and transitions of care. The guidance derived from these protocols should be incorporated into the workflow, usually as prompts and guidance built into structured order sets and documentation forms. Other performance-improvement techniques and high-reliability design measures can dramatically improve the chances that a patient will benefit from the best practices available. Extensive guidance for inpatient glycemic control teams are available at no charge from the Society of Hospital Medicine Glycemic Control Resource Room¹.

Reference

1. www.hospitalmedicine.org, follow Quality/Safety links.

Table 4. Hierarchy of Reliability

Level		Predicted success rate
1	"State of Nature" –no standardization	40%
2	Decision support exists but not linked to orderwriting, or prompts withing orders but no decision support	50%
3	Protocol well -integrated (into orders at point of care)	65-85%
4	Protocol enyhanced (by other QI and high reliability strategies)	90%
5	Oversights identified and addressed in real time	95+%

Glucose Control and (Continuous) Glucose Monitoring in Critical Illness

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Key points

- Stress hyperglycemia occurs in 50% to 80% of critically ill patients and has become an important therapeutic target in critically ill patients.
- Aggressive treatment of hyperglycemia with insulin may be limited by an increased risk of hypoglycemia.
- A factor that may contribute to hypoglycemia is insufficient frequency of glucose monitoring.
- Recent evidence suggests that continuous monitoring of glucose levels may help to signal glycemic excursions and eventually to optimize titration of insulin therapy in the ICU.

Stress hyperglycemia occurs in 50% to 80% of critically ill patients and has become an important therapeutic target in critically ill patients. Hyperglycemia is associated with adverse outcome, not only after myocardial infarction, coronary artery bypass graft, stroke, and trauma, but also in the intensive care unit (ICU). Intensive insulin therapy (IIT) to maintain strict normoglycemia has been shown to reduce morbidity and the length of stay in the ICU and hospital. IIT may be associated with an increased risk of hypoglycemia. The inherent clinical perturbations of critically ill patients result in frequent changes in insulin needs that require extensive efforts from nurses. Current insulin titration is based upon discontinuous glucose measurements, which may miss rapid changes in glycemia. Continuous monitoring of glucose levels may help to signal glycemic excursions and eventually to optimize titration of insulin therapy in the ICU.

Clinical Impact of Hyperglycemia and Benefits of Insulin Therapy in the ICU

The studies of Van den Berghe et al. showed that IIT to achieve normoglycemia reduced the incidence of acute renal failure and accelerated discharge from the ICU and the hospital^{1,2}. In contrast to the surgical ICU, in the medical ICU, in-hospital mortality was reduced only among patients staying for three days or longer. Most likely, the beneficial effects of IIT require time to be realized, because insulin therapy is aimed not at curing disease but at preventing complications. The impact of hyperglycemia on mortality varies depending on the background severity and type of illness.

Whether attainment of strict normoglycemia or administration of insulin is the decisive factor that explains the clinical benefits of IIT is open for discussion. A linear correlation between the degree of hyperglycemia and the risk of death, which persisted after correction for insulin dose and severity of illness, has been demonstrated³.

Aggressive treatment of hyperglycemia with insulin may, however, be limited by an increased risk of hypoglycemia. Recognition of hypoglycemia in a patient who is receiving sedatives and analgesics and/or neuromuscular blocking agents in the ICU is problematic, since the hypoglycemic state may go unrecognized for a critical period before treatment. The German VISEP trial was stopped prematurely because no differences in mortality and frequent hypoglycemia were found in the intensive insulin therapy arm⁴. Interestingly, no adverse clinical outcome associated with hypoglycemia was reported in any study. One factor that may contribute to hypoglycemia is insufficient frequency of glucose monitoring.

Management of Hyperglycemia

To achieve strict glycemic control in critically ill patients, the implementation of insulin infusion protocols based on frequent glucose monitoring is required. First, precipitating causes of stress hyperglycemia should be identified and treated. Second, the patient population in which insulin therapy may be of benefit should be clearly defined. Third, consensus should be obtained regarding the glycemia target level. Fourth, glycemic excursions should be carefully monitored, preferably on a continuous base, and a validated, easily implementable insulin infusion protocol should be provided.

What level of glycemia should be the target? The Society for Critical Care Medicine recently recommended maintaining a blood glucose level of < 150 mg/dL in patients with

severe sepsis⁵. The target glycemia in the Leuven studies was 80-110 mg/dL^{1,2}. Krinsley observed the lowest in-hospital mortality in critically ill patients with a mean blood glucose of 80-99 mg/dL⁶, whereas Finney et al. observed a mortality benefit with a speculative upper limit of 145 mg/dL in cardiothoracic surgery patients⁷. Data are difficult to interpret because of the diverse clinical settings, the varying methods of insulin administration, and different targets of glycemic control. The American Diabetes Association and the American College of Endocrinology have published guidelines recommending in-hospital IIT to maintain preprandial blood glucose levels at ≤ 110 mg/dL in critical care patients⁸. Postprandial glycemia should be kept < 180 mg/dL in any hospitalized patient.

Glucose control and monitoring in the ICU.

Insulin requirements vary widely in patients depending on insulin sensitivity, caloric intake, the nature and fluctuating severity of the underlying illness and the administration of medications. The analysis of the correct amount of insulin to be administered requires a relatively high degree of skill, and frequent expert assessment will be needed as the clinical situation changes^{9,10}.

A standardized protocol that prompts users to initiate an insulin drip for critically ill patients to maintain normoglycemia should be developed. Goldberg et al. proposed a comprehensive, validated insulin infusion protocol (IIP)⁹ that took into account the current and previous blood glucose level to calculate the rate of glycemic change, and the current insulin infusion rate. IIPs add significantly to the work of managing ICU patients. Another obstacle to implementing IIPs is the fear of hypoglycemia in patients being treated. The transition from intravenous (IV) to subcutaneous (SC) insulin should be an integral part of any insulin infusion protocol. This transition can be considered in extubated patients who are taking regular

meals and do not have signs of infections, provided that an infusion of ≤ 3 units/hr is sufficient to maintain normoglycemia.

Current Methods to Evaluate Glycemic Control in the ICU

Glucose indices. To objectively assess glucose control in acutely ill patients, the magnitude and duration of hyperglycemia should be evaluated. Indices of glucose regulation that have been used in acutely ill patients are admission glucose regulation, maximum and mean glucose. However, these indices are based on either a single measurement or on a subset of measurements, and thus are not indicative of overall glycemia and give no indication of blood glucose variability.

Continuous Glucose Monitoring Systems (CGMS) in the ICU

Rationale for use. A continuous display of blood glucose levels seems to be essential for optimal titration of insulin therapy in the ICU. Besides giving an indication of overall glycemia, it shows the variability and fluctuations of blood glucose concentrations which may affect patient outcome.

Technical requirements and validation for the ICU. Data on the reliability of CGMS in diabetic patients cannot be automatically applied to a different situation such as the ICU, where many variables can affect CGMS performance (edema, hypotension, vasoactive drugs, etc.). Necessary requirements for a CGMS include immediate availability of the measurement result, a high frequency of measurements, and fast sensor signal stabilization after application and over time¹¹.

Current CGMS measure glucose in the interstitial fluid. Changes of glucose concentrations in interstitial fluid lag behind those in the blood by a few seconds to up to 15 minutes. The lag time seems to be consistent, irrespective of increments/decrements in glycemia and insulin levels¹²⁻¹⁴. In the ICU, the hemodynamic alterations we encountered (hypotension, shock, vasopressor/inotropic

need) did not worsen accuracy¹⁵. Instead, such variables would affect the process of subcutaneous glucose recovery, resulting in a calibration issue, rather than in a sensor performance issue. A lag time of < 10 min is clinically acceptable since online adjustment of insulin dose occurs every hour and should be based on immediate detection by CGM of unacceptable rates of change (> 25 mg/dL/hour).

CGM accuracy improves with an increasing number of calibration points^{15,16}. Calibration should also be performed in times of glucose stability ($< 10\%$ change in glucose over 9 minutes for the GlucoDay[®], and a rate of change in glucose < 2 mg/dL/min for the CGMS and Freestyle Navigator[®] Continuous Glucose Monitor).

Only a few studies used CGM in critically ill patients^{15,17-20}. In a pilot study using continuous glucose monitoring (GlucoDay[®]) in the medical ICU, rapid changes in glycemia were noted immediately, whereas these were noted much later ($\sim 1-3$ hours) when only intermittent blood glucose determinations were used. Hyperglycemia was present in 74% of medical ICU patients, and target glycemia (80-110 mg/dL) was reached only 22% of the time, which reveals the inadequacy of current insulin protocols to optimize glycemia and suggests the potential of an accurate continuous glucose monitoring system in this setting¹⁵. Similar results were reported by Goldberg et al. using the CGMS device (Medtronic MiniMed Inc., Northridge, CA) in a medical ICU¹⁷. The presence of edema or hypotension, and the use of vasopressors did not affect sensor accuracy. There were no serious adverse events reported during the use of the CGMS. Vriesendorp et al., who used the GlucoDay[®] device during and after surgery, encountered a high technical failure rate¹⁸, which was mainly attributed to breaking of the microdialysis fiber during transfer from the surgical bench to the ICU bed. Using CGMS, Baird et al. observed that acute and final infarct volume change and outcome were negatively affected in patients with mean blood glucose levels ≥ 126 mg/dL¹⁹.

Chee et al. conducted a study to determine if the CGMS device could be used in real-time to control glycemia in five critically ill patients. A closed-loop control system was constructed to use CGMS in a real-time manner, coupled with a proportional integral (PI) control algorithm based on a sliding scale approach for automatic IV insulin infusion. They concluded that the automatic sliding scale approach of closed-loop glycemic control is feasible in ICU patients, but the algorithm needs refinement and the sensor accuracy needs to be improved²⁰.

How to use data obtained with CGM? The vast amount of data collected during CGM must be presented in an understandable way so that the physician can interpret it adequately. First, the CGM System should display the actual (real-time) glucose measurement, and a warning alarm should be available if the actual glucose value is outside a predefined target value. Second, CGM provides trend information, making it possible to predict the course of glucose changes for over longer time periods. Third, CGM data not only highlight the cumulative hyper- and hypoglycemia, but also show glucose fluctuations.

The use of CGMS in critically ill patients looks promising. If further developed as a "real-time" glucose sensor, CGMS technology could ultimately prove clinically useful in the ICU by providing alarm signals for impending glycemic excursions, rendering IIT easier and safer. The development of a closed-loop control system, with an accurate CGMS and computer-assisted titration of insulin dose based on glucose measurements, could permit tight glycemic control without increasing the workload of the nursing staff. Plank et al. observed that, compared with routine protocols, treatment according to a fully automated model-predictive-control (MPC) algorithm resulted in a significantly higher percentage of time within the target glycemic range (80-110 mg/dL)²¹. The European community-funded CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients) project aims

to develop a low-risk monitoring and control system that allows health care providers to maintain strict glycemic control in ICUs using a SC-IV closed-loop system.

Conclusion

Stress hyperglycemia is highly prevalent in the ICU and is associated with adverse outcome. IIT to achieve normoglycemia may reduce mortality and morbidity. Identification of the hyperglycemic patient with timely, cost-effective, and comprehensive evaluation and risk stratification may facilitate appropriate implementation of therapies and procedures that may enhance outcome. Current insulin titration is based upon discontinuous glucose measurements, which may miss rapid changes in glycemia. Recent evidence suggests that continuous monitoring of glucose levels may help to signal glycemic excursions and eventually to optimize titration of insulin therapy in the ICU.

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PROCEEDINGS

Glucose Sensor Technology: Current State and Future Trends

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Key points

- *General agreement now exists that normalization of blood glucose levels through insulin administration is desirable for all hyperglycemic patients.*
- *Delivering insulin safely (to avoid hypoglycemia) and effectively (to achieve the increasingly strict glucose targets) requires meticulous monitoring of blood glucose levels, and glucose sensors are a critical component of an effective glucose control system.*
- *Compared with standard, intermittent glucose checks, continuous glucose monitoring provides far more frequent checks, which can more promptly detect important trends in blood glucose levels.*
- *The Food and Drug Administration limits current glucose-sensor technology to adjunctive use, because of a time-lag effect caused by various factors.*
- *Other approaches to blood glucose measurement being explored include extracorporeal methods, indwelling venous catheters, and non-invasive optical technologies—all of which require further testing before they can be used in critical-care populations.*
- *Ultimately, closed-loop, continuous glucose monitoring systems are likely to replace all of the labor-intensive protocols currently in use and will be a key factor in improving hyperglycemia therapy.*

Normalization of blood glucose levels is now generally considered desirable for all hyperglycemic patients. Achieving this goal frequently requires the use of insulin, particularly in hospitalized patients. Delivering insulin safely (to avoid hypoglycemia) and effectively (to achieve the increasingly strict glucose targets) requires meticulous monitoring of blood glucose levels. Glucose sensors are a critical component of an effective glucose control system.

Compared with the current standard of care that uses intermittent glucose checks, continuous glucose monitoring offers far

more frequent monitoring. Hyperglycemic patients present complex clinical challenges, and less-frequent monitoring can fail to detect important trends promptly.

Current State

In principle, an effective continuous glucose monitoring system (CGMS) uses a glucose electrode with the following characteristics: 1) specificity for glucose, 2) sensitivity for glucose, 3) a favorable signal-to-noise ratio, 4) accuracy, and 5) precision. Today, most glucose electrodes are glucose-oxidase (GO) based. Using additional innovative technologies such as selectively permeable mem-

branes, these sensors are now available commercially to assist in the outpatient management of diabetes.

Current CGMS require initial calibration to an external reference, either a laboratory value or, more commonly, a point-of-care (POC) glucose-monitor result. If the latter reference is used for calibration, the lower precision of POC monitors may contribute to CGMS inaccuracy. In addition, most electrodes exhibit drift over time and require recalibration. Thus, stability is also an important glucose-electrode characteristic.

Today the most prevalent approach is interstitial fluid sensing, done either by a “needle”-type sensor or a microdialysis catheter inserted subcutaneously. With these systems, when glucose values change rapidly, there may be differences between sensor values and a reference method. For example, with the microdialysis method, the length of the catheter and, thus, the time required for the fluid to arrive at the sensor creates a delay (usually in minutes) that must be taken into account. Device software that averages values to improve accuracy also may cause delays. Finally, an “alternate-site-testing-like effect” has been described. This term refers to a variable time lag that was first reported with standard, intermittent, POC monitoring, when sampling sites other than fingertip (e.g., forearm) were tested. Because of this time-lag effect, FDA clearance for current glucose-sensor technology is limited to adjunctive use.

Future Trends

Several companies have used an extracorporeal approach that withdraws venous blood from the patient for measurement. Earlier techniques (Biostator® glucose-controlled insulin-infusion system, Miles Laboratories) did not return the blood to the patient and could lead to anemia. Newer methods return the blood to the patient.

Indwelling venous catheters are also being studied, but these have the potential for thrombus, embolism and infection. All of these more-invasive methods may eliminate the delays seen with less-invasive monitoring and have the potential to simplify the control system algorithms. Entirely non-invasive approaches (mostly optical methods utilizing near-infrared spectroscopy) are also being explored. Due to the complexity in distinguishing the glucose signal, progress has been slow.

Most sensor research has involved patients who are not acutely ill. Critically ill patients in the intensive care unit (ICU) are more complex. They exhibit hemodynamic instability and variable perfusion, and usually are treated with many medications. For this reason, clinical trials must be performed in this population prior to adopting the technology in this setting.

Ultimately, glucose sensors will routinely serve as the input systems to closed-loop glucose control therapy. Once the control system algorithms have been clinically validated and safety concerns have been addressed, these closed-loop systems are likely to replace the labor-intensive protocols currently in use.

Summary

Current developments in glucose monitoring sensors are promising and clinical trials are underway. The future of emerging, entirely non-invasive technologies, such as optical or spectroscopic systems is still uncertain; however, other minimally invasive and invasive techniques are promising. They have the potential to decrease the staff workload inherent in frequent glucose monitoring and, therefore, will be key to enabling nurses to implement hyperglycemia therapy. Reduced blood glucose variability and rates of hypoglycemia that result from more frequent glucose monitoring, in turn, are likely to be associated with better outcomes and greater patient safety.

PROCEEDINGS

Assessing the Accuracy and Confounding Factors in Critical Care Glucose Monitoring

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Key points

- As the use of point-of-care (POC) glucose monitoring systems (GMS) for tight glycemic control (TGC) becomes more common in critically ill patients, the accuracy of the information from instruments is important.
- Physiologic factors that can affect accuracy include hematocrit, blood pO_2 , blood pressure, sample source (venous, arterial, capillary), pH, temperature and the blood matrix (water, lipid, cellular, and protein contents).¹
- Other factors affecting accuracy include drug interferences, user error and harsh environmental conditions.
- There are many methods to evaluate the accuracy of POC glucose meter readings, including national and international standards, and illustrative and statistical methods to determine if a GMS is comparable to a reference instrument.
- Manufacturers must continue to develop measures to adjust for factors that affect accuracy, and healthcare professionals should be aware of the limitations of the GMS they use and evaluate accuracy.
- New range-specific analytical methods are needed to assess the accuracy of GMS at hypoglycemic, normoglycemic and TGC ranges.

There is a need to address factors affecting the accuracy of point-of-care (POC) glucose monitoring systems (GMS). Several studies have shown that factors such as pO_2 and hematocrit affect GMS accuracy. More recently, new instruments that adjust for these types of factors have shown improved performance characteristics of the devices.¹ Factors affecting accuracy may cause different effects based on the detection method used by a specific POC GMS. GMS commonly use enzymes such as glucose dehydrogenase (GD) or glucose oxidase (GO) in their biosen-

sors and rely on amperometry or photometry to measure glucose. The blood sample types used in different devices may also vary. Most systems are designed to accept capillary, arterial or venous blood samples, which make them convenient tools for tight glycemic control (TGC). With the frequent use of POC glucose monitoring for TGC in critically ill patients, there is a need for accurate instruments that are resistant to the factors affecting accuracy. The purpose of this article is to provide a brief overview of these factors and how to evaluate GMS accuracy.

Factors Affecting Accuracy

Exogenous and endogenous factors affect the accuracy of GMS. Endogenous factors include specific physiological elements such as hematocrit, blood pO_2 , blood pressure, sample source (venous, arterial, capillary), pH, temperature and the blood matrix (water, lipid, cellular and protein contents)¹. Exogenous factors include drug interferences, user error and harsh environmental conditions. In this article we highlight factors that may cause errors in glucose monitoring.

Hematocrit. The amount of red blood cells relative to plasma has an inverse effect on measured glucose. Dacombe et al. found that increases in hematocrit cause decreases in glucose readings². Conversely; decreases in hematocrit were found to increase glucose values. The mechanisms that cause this effect may be diffusion-related or mechanical in nature. A high hematocrit can decrease the amount of glucose that diffuses into the biosensor. The large amount of red blood cells in high-hematocrit samples may also mechanically impede the biosensor and reduce glucose readings. Low-hematocrit samples can cause increased diffusion of glucose towards the biosensor, thereby leading to higher readings on the GMS. Some instrument manufacturers address the hematocrit problem by pre-lysing red blood cells before testing or by compensating for hematocrit effects using software algorithms¹.

pO₂ effects. Critically ill patients may be receiving oxygen therapy and blood pO₂ levels may be higher than normal. GO-based systems originally had inaccuracies at extreme pO₂ levels. This was common in systems that relied on reactions that generated a hydrogen peroxide intermediate. Hydrogen peroxide then disassociated into hydrogen ions, oxygen and electrons (used to measure glucose)³. As pO₂ increased (>100 mmHg), the disassociation reaction would become less favorable and thus cause lower glucose readings. Recent GO-based systems no longer use an oxygen intermediate, thereby minimizing or eliminating this confounding factor. The opposite may also be true, where low pO₂ (<40 mmHg) can affect glucose results by 15% when using GO-based systems⁴.

Hypotension and hypoperfusion. Sylvain et al. showed GD-based systems have significantly different results ($p < 0.001$) when testing capillary whole blood samples from hypotensive patients compared to a reference analyzer⁵. GO-based systems showed similar results. In contrast, venous samples tested on GMS did not show statistically significant differences when compared to venous samples tested using laboratory analyzers.

Sample source. Capillary blood is the most common sample used for POC GMS. Several studies have shown variations in accuracy when comparing capillary versus venous blood samples⁶. Recent GMS showed greater accuracy with arterial samples compared to capillary blood. In contrast, older GMS models showed similar results between the two sample types. Results derived from venous blood samples exhibited improved accuracy compared to capillary blood for GD-based GMS.

Specimen matrix. Water, lipid, protein and cellular content may also affect accuracy. Glucose is more soluble in water and high plasma water content can cause higher glucose readings⁷. Lipid, proteins and cel-

lular components may impede photometric systems by increasing the turbidity of the sample. Such matrix effects may also alter the viscosity and hence reduce the glucose diffusion rate in both amperometric and photometric systems.

Drugs. Drugs that can oxidize or reduce glucose biosensor electrodes can also interfere with glucose results. Tang et al. determined the effect of 30 different drugs on six different glucose meters⁸. High doses of ascorbic acid were shown to yield lower glucose values on GO-based systems. Acetaminophen caused increased glucose values in all tested GD-based systems and in some GO-based systems. High doses of dopamine increased glucose values in GD-based systems. Mannitol increased glucose values in GO-based systems. Icodextrin has been shown to generate falsely high glucose readings because the drug being metabolized to maltose, which is indistinguishable from glucose with GD-based instruments⁹.

pH and temperature. Since most GMSs use enzymes to catalyze the conversion of glucose into a detectable signal, pH and temperature may play a role in altering the enzyme kinetics, thereby causing errors. Kilpatrick et al. found significant deviation in glucose measurements for samples with $pH < 6.95$ and > 7.85 ¹⁰. More recently, a new 5mg/dL median absolute difference standard has been proposed. This standard is based on a locally smoothed median absolute difference curve, a non-parametric mathematical method to identify trends and biases within large datasets²⁰. Temperature can also play a role. Oberg et al. suggest that cold temperatures may also produce discrepancies but the effects of fever are currently unknown^{4,11}.

Other factors. User error and environmental conditions can also affect accuracy. Studies have shown that the potential for operator error still exists despite advances in more user-friendly instruments and pro-

ocols¹². Environmental conditions have also become more important with the use of POC instruments under field conditions (e.g., disaster areas, war zones, rural areas). POC instruments, including GMS, were used on airborne hospitals to evacuate survivors after the Asian Tsunami of 2004¹³. Kost et al. have suggested that conditions in post-Tsunami Thailand and post-Hurricane Katrina New Orleans were unacceptable for POC GMS use because of high humidity and temperatures. This has been verified by a study that tested the robustness of POC instruments under certain environmental stresses¹⁴.

Accuracy Assessment

Methods are available to evaluate the accuracy of POC glucose meters. These include national and international standards, as well as illustrative and statistical methods to determine if a GMS is comparable to a reference instrument. Illustrative methods such as mountain plots, Clarke Error Grid, and Bland-Altman plots are commonly used. These illustrative methods may be coupled to standards such as the Clinical Laboratory Standards Institute (CLSI) and International Organization for Standardization (ISO) 15197 criteria^{15,16}. Examples of statistical methods to evaluate accuracy include the Student's *t*-test, analysis of variance (ANOVA), and least squares linear regression.

Illustrative methods. These methods allow for quick determination of biases, trends and errors. The mountain plot, also called an empirical cumulative distribution plot, allows for easy identification of the central 95% of the data and provides clearer differentiation of two distributions (e.g., GMS versus reference)³. It is generated by computing the percentile for each ranked difference between the GMS and the reference. The plot shows the median bias between the two methods, while the tails of the plot show the propensity for the new method to deviate from the reference method.

The Clarke Error Grid divides a scatter plot (GMS versus reference) into five zones (A, B, C, D, and E)¹⁷. Data points falling into zones A and B are considered acceptable, while data falling into zone C indicate the GMS' results may prompt unnecessary corrections. Zone D represents dangerous failure to detect a glucose level and Zone E represents results causing erroneous treatment. There has recently been the introduction of the continuous glucose error grid that allows a user to evaluate the accuracy of continuous glucose monitors. The five zones are retained but the shape of the error grid allows the investigator to also evaluate the glucose rate (e.g., blood glucose as a function of time)¹⁸.

The Bland-Altman plot is a bias plot (bias versus reference)¹⁹. This method is useful in that it shows biases, trends, and errors. When coupled to the CLSI or ISO 15197 standards, these plots serve to identify if an instrument meets the acceptance criteria.

Accuracy standards. The CLSI and ISO 15197 standards are often cited in literature when comparing laboratory instruments^{3,15,16}. For example, the ISO 15197 standard uses the measurement of glucose concentrations from capillary blood samples and provides procedures to verify and validate performance. The ISO criteria requires 95% of the data points to have a bias of ± 15 mg/dL at reference glucose levels of < 75 mg/dL. For reference values ≥ 75 mg/dL, the bias must be within $\pm 20\%$ of the reference value. In contrast, the CLSI standard requires the bias to be ± 15 mg/dL for values < 100 mg/dL. For values ≥ 100 mg/dL, the bias must be within $\pm 20\%$ of the reference. Originally the ISO standard was commonly used outside the United States. More recently, an October 2006 draft Food and Drug Administration (FDA) guideline describes the use of the ISO 15197 criteria for GMS²⁰.

Statistical methods. Statistical tests can provide p-values or correlation coefficients. The Student's *t*-test is an example of one statistical test.³ There are three kinds of *t*-tests: one-sample, two-sample, and the *t*-test for paired differences. For the purposes of comparing a GMS versus a reference analyzer, the Student's *t*-test for paired differences is used, since results from the same blood sample are being compared. The Student's *t*-test for paired differences assumes that the samples are not independent (e.g., using the same blood samples) and the data are distributed normally.

ANOVA is another statistical method, which compares the differences of three or more groups of data. This is very useful for comparing variations between different GMS test strip lots. Both the Student's *t*-test and ANOVA generate a *p*-value, where $p < 0.05$ is usually considered statistically significant²¹.

Least squares linear regression, commonly referred to as linear regression, generates a best-fit line onto a scatter plot (GMS versus reference analyzer)³. The correlation coefficient (*r*), coefficient of determination (*r*²), and equation of the line are generated on this plot. The *r*²-value is commonly used, with *r*² ranging from 0 to 1, where 0 indicates a non-linear relationship and 1 is a perfect fit. Manufacturers strive to attain a very high *r*²-value, because it indicates high correlation between GMS and the reference. However, it must be noted that least squares linear regression is very susceptible to the weighting effects of data points at extreme values. For example, if a single value at a high reference range falls on the regression line, it may provide a high *r*²-value. Removal of this data point may then reveal the less-than-satisfactory nature of a dataset. Therefore, investigators must be aware of the potential for data to have poor agreement but still produce relatively high correlations.

Conclusions

Manufacturers must continue to develop measures to adjust for confounding factors, and healthcare professionals need to be aware of the limitations of the GMS they use. There are methods to evaluate accuracy that are useful but may be misleading. Instruments may show good correlation to a reference standard, but this may not mean that the results show agreement when using other methods such as linear regression. As instruments accommodate factors affecting accuracy through biosensor and software design, there may be a shift towards newer, stricter methods to evaluate the accuracy of GMS. Given the heterogeneity of physiological conditions present in critically ill patients, factors affecting accuracy may play a much larger role in trying to achieve TGC. Accuracy at the low-ranges, especially for pediatrics and neonates, are also important considerations. High accuracy near and within the TGC ranges is also necessary for reliable glucose monitoring in TGC protocols. Therefore, new range-specific analytical methods are needed to assess the accuracy of GMS at hypoglycemic, normoglycemic and TGC ranges.

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PROCEEDINGS

Glucose Sensor Augmented Insulin Delivery in the Hospital: Open and Closed-Loop Methods

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Key points

- *Frequent monitoring is required to effectively control blood glucose levels with a low incidence of hypoglycemia; however, current manual methods of blood glucose monitoring are labor-intensive, costly, prone to error and expose the caregiver to potentially infectious blood.*
- *A safe, effective and user-friendly medical device that automatically and continuously monitors the concentration of glucose in hospitalized patients is greatly needed.*
- *Continuous glucose monitoring systems are being developed for hospital use that measure glucose in the blood or interstitial tissue fluid.*
- *Although a fully closed-loop automated system seems desirable for the hospital setting, safety and regulatory issues need to be overcome.*
- *A major step forward for in-hospital blood glucose control would be a system with a bedside monitor that organizes all important clinical data for glucose control in one real-time display and a computer algorithm to recommend an appropriate insulin infusion dose according to glucose trend data.*

The prospective studies by Van den Bergh et al. focused attention on the importance of glycemic control in medical and surgical patients requiring intensive care^{1,2,3}. Retrospective studies of patients in the intensive care unit (ICU)⁴⁻¹³ revealed a marked decrease in morbidity, mortality, length of stay and cost when blood glucose is controlled in the near-normal range with intensive insulin therapy (IIT) methods. Recent clinical trial evidence suggests a correlation between high blood glucose variability and increased morbidity and mortality¹⁴⁻¹⁵. Although not all trials using IIT for glucose control have demonstrated an improvement in clinical outcome¹⁶⁻¹⁸, the majority of studies in ani-

mal and human suggest that even mild to moderate hyperglycemia can adversely affect immune function and cell survival following ischemia¹⁹⁻²¹. In contrast, one recent study documented an increased risk for stroke and death when a patient's high glucose levels were rapidly lowered to normal levels during general anesthesia and cardiac surgery²².

Need for Frequent Monitoring

Frequent monitoring is required to effectively control blood glucose levels with a low incidence of hypoglycemia. Current manual methods of blood glucose monitoring are labor-intensive, costly, prone to error, and expose the caregiver to potentially infectious blood.

The average time required for a nurse or technician to acquire a blood sample and measure the concentration of glucose using a point-of-care meter has been estimated to be 4.7 minutes²³. Thus, one to two hours of a hospital employee's time per day is required to monitor the blood glucose concentration of a patient being managed with IIT.

IIT methods have been plagued by an unacceptably high rate of hypoglycemia²⁴. All clinical trials published to date report a higher incidence of hypoglycemia in the IIT group compared to the conventional treatment group²⁵⁻³⁰. The fear of hypoglycemia and the increased morbidity and mortality associated with hypoglycemia remains the major barrier to the clinical application of IIT protocols in the hospital setting.

A safe, effective and user-friendly medical device that automatically and continuously monitors the concentration of glucose in hospitalized patients is greatly needed. Real-time glucose monitoring will provide important trend information: absolute concentration (mg/dL, mmol/L), direction of change (stable, increasing or decreasing), and rate of change (stable, slow or fast). The trend information can be used by the bedside nurse to titrate the delivery of insulin and/or glucose to maintain blood glucose in the desired range. The risk for hypoglycemia will be minimized and or eliminated.

Continuous glucose monitoring (CGM) systems are being developed for use in hospitals that measure glucose in the blood or

interstitial tissue fluid (ISF). Some glucose sensors are inserted directly into the subcutaneous tissue or blood stream and other CGM systems automatically deliver a sample of ISF or blood to a glucose sensor external to the body³¹⁻³².

Blood Glucose Monitors

The Via® Blood Chemistry Monitor for Glucose (VIA) shown in Figure 1 was developed by VIA Medical Corporation (San Diego, CA) in 1991 to automate the process of blood glucose monitoring in the hospital setting. This device received Food and Drug Administration approval to measure the concentration of glucose as frequently as every 5 minutes for 72 hours using blood sampled from a radial artery catheter, a peripheral venous catheter or the proximal port of a central venous catheter. The system automatically delivers a sample of patient blood to an external flow-through glucose sensor using a bi-directional infusion pump³³⁻³⁵.

The sensor measures the blood glucose concentration using glucose oxidase to produce hydrogen peroxide. Each sample is automatically infused back into the patient, avoiding blood loss and caregiver exposure to bodily fluids. VIA sensors tested in-vivo demonstrate high sensitivity, accuracy ($R^2 = 0.997$) over the physiological range (30 to 600 mg/dL), specificity for glucose and lack of sensitivity to changes in oxygen and hematocrit.

The calibration solution is continuously infused through the tubing and sensor at a rate of 5 mL/hour. Before each blood glucose measurement, the monitor performs a one-point calibration using the Isolyte-glucose solution (83 mg/dL) as the reference. The acquired blood sample remains within the sensor and tubing for approximately 50 seconds. The sample is then flushed back into the bloodstream with 6.0 mL of Isolyte-glucose solution. The volume of fluid infused by VIA may be excessive for many hospital-

Figure 1



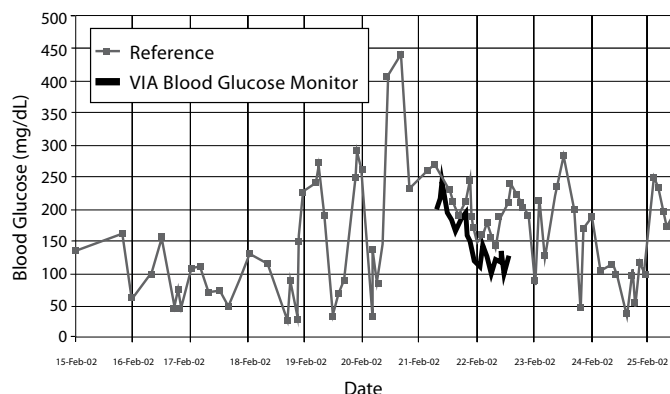
VIA Blood Chemistry Monitor for Glucose attached to vascular catheter in peripheral vein. Vascular catheter connected to sterile tubing, flow-through glucose sensor and Isolyte-glucose calibration solution. Bedside monitor contains user controls, bi-direction infusion pump, air bubble sensor, pressure sensor, data display, auto-sampler and printer. Sensor housing and cable are attached to the patient's left arm with tape.

ized patients with cardiac and renal disease. Glucose measurements using a VIA glucose monitor are shown in Figures 2 and 3.

All external flow-through sensors have problems with blood vessels and indwelling catheters when blood samples are obtained frequently over an extended period of time. Repeated sampling from the peripheral vein of an ICU patient can be a problem because of low flow, vessel wall collapse, obstruction from a valve, vessel thrombosis and catheter occlusion due to clot, fibrous tissue and kinking³⁶⁻³⁷. Attaching the VIA to a radial artery catheter will overcome some of these limita-

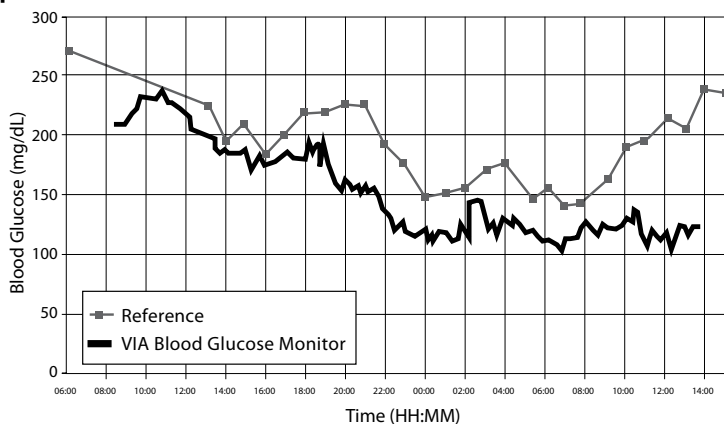
tions, but vessel thrombosis and clot formation within the catheter lumen remain a clinical problem³⁸⁻⁴⁰. The ability to frequently sample blood from a central venous catheter (CVC) over time using the VIA has not been validated. The lumen of the CVC will be exposed to static blood for 60 minutes per day when sampling once every 20 minutes, possibly leading to catheter obstruction (50 seconds x 3 samples/hr x 24 hours = 3,600 seconds). The VIA sample can be contaminated with glucose-free or glucose-containing solutions being infused through the tubing. The sample can also be contaminated with fluids infused through an adjacent CVC port.

Figure 2. Type 1 Diabetic—Leg Ischemia



Glucose control in hospitalized patient with type 2 diabetes requiring 80 units of insulin/day. Note glucose variability using fingerstick measurements and intermittent subcutaneous insulin injections (—■—). VIA glucose monitor used to adjust IV infusion of regular insulin during anesthesia and major vascular surgery (—■—).

Figure 3. Glucose Sensor Augmented Insulin Delivery
Open-loop



Close-up of glucose measurements using VIA glucose monitor attached to a peripheral vein of a diabetic patient undergoing major vascular surgery. Fingerstick glucose measurements were obtained once hourly (reference). IV insulin infusion was titrated by an experienced anesthesiologist.

Interstitial Tissue Fluid Monitors

Many are quick to discount the clinical utility of needle-type glucose sensors inserted into the subcutaneous tissue of hospitalized patients. Issues with tissue edema, physiological differences between blood and ISF glucose, variable time delays following a step change in glucose, variable changes in tissue oxygen concentration and blood flow and potential interfering substances have been cited as concerns.

Preliminary data in hospitalized medical and surgical patients, however, has encouraged further research. Comparison of glucose sensor data with reference arterial, venous and capillary glucose data have yielded mean absolute relative difference (MARD) and correlation coefficient values that are clinically acceptable^{31,32,41,42}.

Current needle-type sensors provide an acceptable estimate of ISF glucose trends. Bedside nurses will be able to combine the CGM trend data with intermittent reference blood sample glucose measurements to improve the titration of insulin (Figure 4). This combined approach should improved overall glucose control while decreasing the risk of hypoglycemia. Fewer blood samples and less

bedside glucose testing should equate to less nursing time.

The major advantage of the needle-sensor technology is the ease of insertion into the subcutaneous tissue. Although typically implanted in the loose connective tissue of the abdomen, insertion in the thigh, arm, chest (Figure 5) and buttock are also possible.

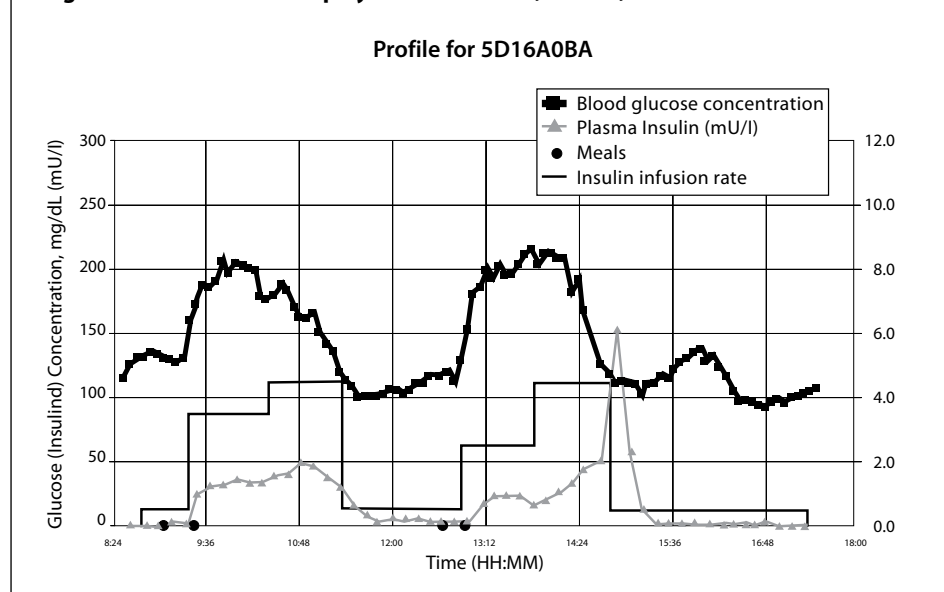
ISF sensors overcome the limitations of blood-based glucose sensors, such as lack of vascular access, vessel occlusion, sample contamination and infection.

Recent studies have used an analysis of multiple simultaneous glucose sensor output signals to improve accuracy and robustness in the clinical setting. An array of sensors implanted in more than one location can be used to ensure a steady stream of glucose data with accuracy superior to an individual sensor implanted in one location. Miniaturization of the sensor and electronics is required to make this concept practical in the clinical setting⁴².

Closed-loop System

The Biostator commercialized by Miles Laboratories in the 1970s demonstrated the feasibility of continuous blood glucose monitoring and closed-loop feedback control of glucose levels. Although a fully closed-loop automated system seems desirable for the hospital setting, safety and regulatory issues need to be overcome. Sensor inaccuracies, time delays in glucose sensing, time delays in IV insulin pharmacodynamics and loss of

Figure 4. Bedside Data Display Glucose Sensor, Insulin, Meals



Flat-panel display visualizing VIA glucose monitor trend data (■), intravenous insulin infusion trend data (▲) and actual venous blood insulin levels (ELISA method). Type 1 diabetes patient consumed breakfast at 8:50, lunch at 12:50 and exercised on a bicycle at 16:00.

real-time data are problems when used in the real-world setting. Successful application of a CGM system that is accurate and robust in the hospital setting will overcome the major technical obstacles of a fully closed-loop system.

Conclusion

There is great clinical need in the hospital for a continuous glucose monitoring system that is safe, accurate, robust and user-friendly. Although our ultimate goal is the development

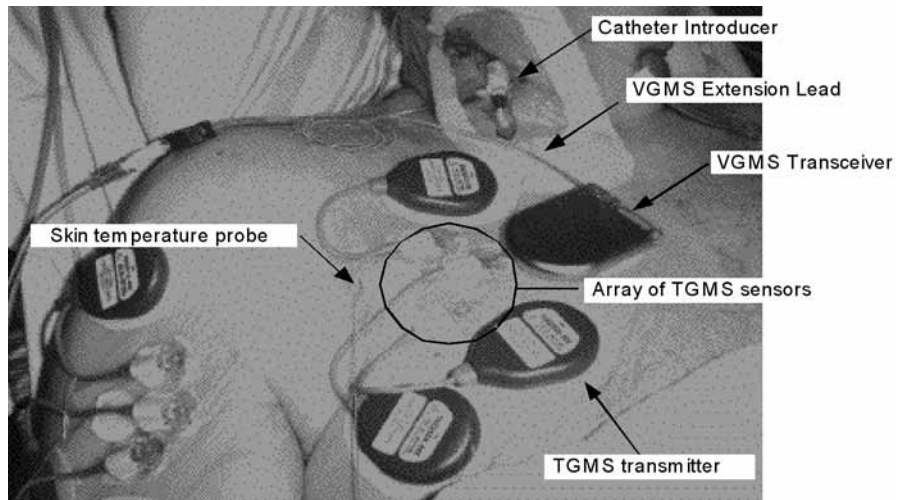
Key to the clinical success of glucose sensor augmented insulin delivery is a CGM system that works well in a broad range of patient populations and hospital environments. Although interstitial fluid and blood-based glucose sensors have shown great promise in the hospital setting, ongoing research is needed to optimize their clinical use^{43,44}.

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Figure 5. Continuous ISF glucose monitoring

1440 measurements/day vs. 4



Medtronic MiniMed needle-type CGM inserted into right upper arm (3 sensor array) and anterior chest (3 sensor array) of type 2 diabetes patient undergoing major surgery. Medtronic Vascular Glucose Monitoring System (VGMS) inserted through central venous catheter into superior vena cava.

Bedside Monitor

A major step forward for in-hospital blood glucose control would be a bedside monitor that displays the real-time CGM glucose trend data, insulin delivery data and enteral/parenteral nutrition delivery data. Organizing all of the important clinical data for glucose control in one real-time display would help the bedside nurse titrate insulin, glucose and meals. A computer algorithm similar to the commercially available GlucoScout or EndoTool[®] could be used to recommend an appropriate insulin infusion dose based on glucose trend data. Advanced algorithms will consider IV insulin kinetics/dynamics, meal models and real-time parameter adjustments for acute changes in insulin sensitivity, drugs and major stress (steroids, catecholamines, sepsis and cardiopulmonary bypass).

of a closed-loop artificial pancreas capable of controlling glucose levels in a narrow range safely and automatically, our immediate goal is to provide the bedside nurse with real-time glucose, insulin and meal information that is organized and analyzed in a clinically useful way. Alarms will alert the caregiver when glucose levels exceed a programmable threshold and increase or decrease at a high rate of change. Smart computer algorithms will recommend the most appropriate management of the patient over a wide range of clinical situations. Nurses will utilize this real-time information to optimize the delivery of insulin in relation to the clinical needs of the patient. Glucose levels will be better controlled and the risk for hypoglycemia will be minimized or eliminated.

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PROCEEDINGS

The Impact of Intensive Insulin Therapy on Nursing

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Key points

- Intensive insulin therapy (IIT) results in an increase in nursing workload.
- Approximately two hours of direct nursing time per patient may be devoted to glycemic control activities in a 24-hour period.
- Approximately \$250,000 in costs was associated with IIT in one intensive care unit in one year for nursing activities, blood glucose testing and supplies.

As tight glycemic control (TGC) with intensive insulin therapy (IIT) has become more common in the intensive care unit (ICU), a change in nursing activities has evolved to incorporate this initiative into patient management. Intravenous (IV) insulin is being used more often to control blood glucose, since subcutaneous insulin is less effective because of variable absorption in the critically ill patient. Administering IV insulin requires more intensive blood glucose monitoring to avoid dangerous glycemic excursions and to meet target glucose levels. Hourly or more frequent checking of blood glucose and frequent adjustments and titration of insulin typically are required, particularly when beginning IV insulin therapy and when the patient has not reached blood glucose target levels.

Critical care nurses already have frequent monitoring, measurement and treatment activities on an hourly basis. The additional tasks required to manage blood glucose significantly increase nursing workload.

When glycemic control initiatives were implemented at our organization, nurses

at the bedside voiced concerns when they attempted to work glycemic control measures into their hourly routines. Many indicated that this was difficult to accomplish because of the time and effort required.

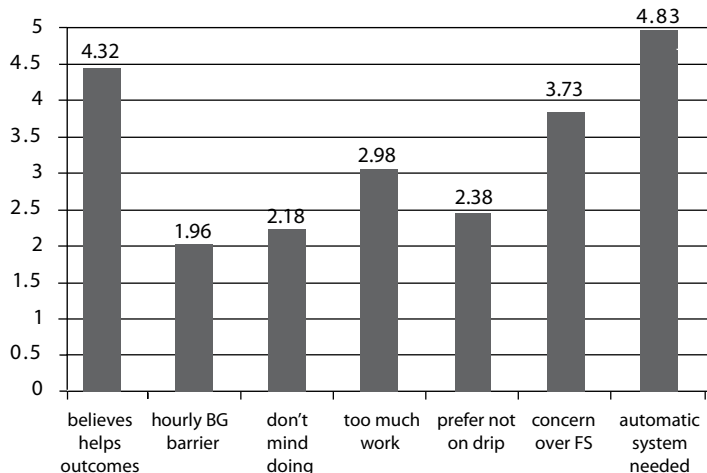
Impact of TGC on Nursing

A study was initiated to evaluate the impact of TGC on nursing workload¹. The purposes of the study were to evaluate the

time and activities involved in hourly glycemic control activities, nursing perception of TGC, and the estimated costs of glycemic control. Another purpose of the study was to get input from nurses about potential use of continuous IV methods to monitor blood glucose, since many companies are developing this technology¹.

The study setting was six ICUs with a total of 58 beds in a level I trauma center in the southeastern United States. The study was descriptive and exploratory in nature. Time and motion methods were used to observe nurses performing glycemic control activities. Surveys were distributed to 122 nurses that used a five-point Likert scale, structured questions about perceptions of glycemic control and open-ended questions for comments. Information on the number

Table 1. Survey Results¹
(1-5 scale – 3 = moderate agreement)



of point-of-care (POC) blood glucose tests, costs for materials and supplies, and nursing salaries was obtained from existing hospital databases¹.

Survey Results

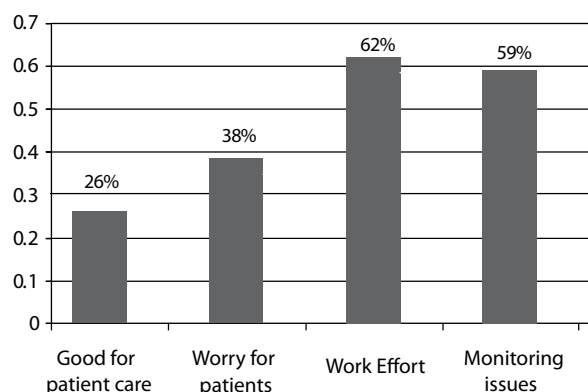
Sixty-six of 122 nurses (54%) completed the survey. Key findings are shown in Tables 1-4. Nurses strongly agreed that glycemic control is an important aspect of patient care that affected outcomes. They also felt glycemic control activities required extensive time and increased workload. They also were concerned about the number of fingersticks required in some patients to obtain blood glucose readings for IIT. They strongly indicated that more automatic and continuous sampling technological methods were needed and that they would be willing to devote an IV access site for that purpose. When asked, 90% of the nurses indicated that rather than delegating activities to ancillary clinical technicians, they preferred to perform their own blood glucose measurement to have better control over the process and greater certainty of the results before titrating IV insulin. Other survey comments were that nurses felt the extra workload associated with glycemic control competed with other tasks performed on an hourly basis, particularly when nurses were assigned more than one patient being given IV insulin. Having to focus on these time-sensitive glucose control activities sometimes took them away from other things they could be doing for the patient¹.

Nursing Work Time and Costs

Up to 32 steps that could be part of hourly glycemic control activities were observed during the study. There was considerable variation in how nurses performed blood glucose testing. Nurses sometimes took shortcuts such as omitting hand hygiene or not wearing gloves to decrease the time needed to do these procedures. With an average time of 4.72 minutes (range 3.13-8.15 minutes)

Table 2. Answers to Open-ended Questions¹

Survey (n=66)



for one hourly round from testing to documentation, one patient on IV insulin requires approximately two full hours of direct nursing time during a 24-hour period. Based on nursing salaries, the number of POC blood glucose tests, costs of testing supplies, quality control tests and average nursing time, the costs to perform glycemic control activities in our hospital's ICU was conservatively estimated to be \$250,000 per year (Table 4). The steady increase in the number of POC blood glucose tests over the year (Figure) further confirmed the increased time spent in measuring blood glucose as IIT was being administered¹.

Discussion

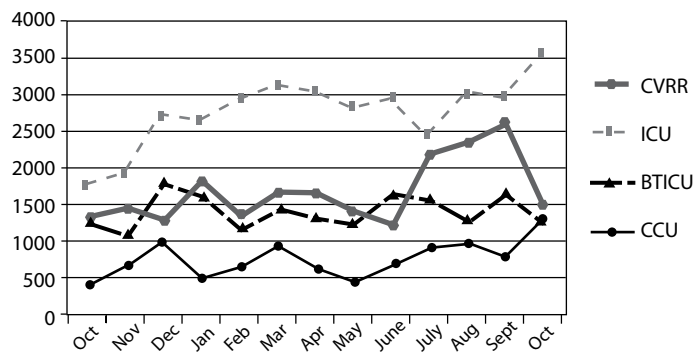
Is all the work worthwhile? Studies conducted by Krinsley² and by Van den Berghe³ both showed decreased patient care costs

and length of stay associated with improving glycemic control. Other possible financial benefits of glycemic control could be realized through reduction in morbidity and mortality, improved patient outcomes, fewer complications and improved resource utilization in the critically ill patients.

Elements that can facilitate the implementation of glycemic control efforts include having an excellent, passionate leader to keep the initiative going; forming a multidisciplinary team to guide and lead the directive; and obtaining input from potential stakeholders in the project. Nurses at the front line need to be included in planning efforts for glycemic control, so that they have an opportunity to provide input into the process and streamline their work.

Figure. POCT BG tests 1 yr¹

n = 85,530



Conclusion

While nurses felt that glycemic control was important for the patient, they also felt that there was considerable extra work involved. The costs associated with glycemic control efforts were substantial. Providing nurses with a continuous and/or non-invasive method for blood glucose measurement was well accepted by nurses as a potential solution to the increased work associated with POC testing.

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Table 3. Cued Responses¹

Checked y/n what applied)	%	N
Too much work	24	16
Takes too much time	44	29
Is a waste of time	6	4
Easier if automated	86	56
Like doing it	1.5	1
Is not difficult to do	38	25
Normal part of patient care	45	30
Should be done by other than RN	15	10
Willing to dedicate an IV line if automated and displayed	76	50
Who performs BG monitoring for patients on IV insulin infusions?		
	RNs—90%	
	Clinical technicians—10%	

Table 4. Findings: Summary¹

- About 2 hours direct nursing care to perform glycemic control related activities
- Nurses believed glycemic control was beneficial for patient outcomes
- Increases the number of BG tests and calibrations done
- Estimated cost of around \$250,000 of nursing time and supplies for one hospital

PROCEEDINGS

Nursing Education and Intensive Insulin Therapy

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Key points

- Core competencies related to TGC and diabetes care include the proper use of insulin and other diabetes medications, medical nutrition therapy, point-of-care testing, hypoglycemia treatment and concomitant therapies.
- Establishment of an interdisciplinary Acute Care Diabetes Advisory Committee was the first step in a quality improvement process.
- A thorough assessment of each professional discipline's current level of knowledge and skills is essential to the development of a strategic plan for glycemic-management education.
- Challenges include nurses' varied work schedules, "information acquisition fatigue," budget constraints and need for administration to understand and support the concept of training to competency rather than to a specific period of time.
- An educational plan for diabetes management and tight glycemic control can include employee orientation, tests of medication knowledge, preceptor guidelines and curriculum, annual competency testing for all disciplines, continuing education and remedial support.
- A creative and innovative approach to education is welcomed by staff and more effective for sustained professional growth.

Ensuring the professional competency of the entire clinical staff is essential to successfully delivering evidence-based, safe, effective, respectful and appropriate diabetes care. In this article, key elements of a successful inpatient glycemic management educational program are reviewed, including core competencies, knowledge assessment, development of a strategic educational plan and continuing education.

Since nursing comprises the largest number of staff members at the frontline of care delivery and the nurse is critical to the success of diabetes care improvement initiatives, this article focuses on nursing educa-

tion. However, the information applies to all healthcare disciplines, including pharmacy, nutrition and medicine.

Inpatient Glycemic Management Improvement

The University of Minnesota Medical Center (UMMC), Fairview, initiated an inpatient glycemic management improvement project in August, 2000. The average daily census is 1,000 and 47% of the inpatient population develop hyperglycemia.

The first step in quality improvement process was to establish an interdisciplinary Acute Care Diabetes Advisory Committee, co-

led by an endocrinologist and an advanced practice nurse. Composed of individuals who had a passion for diabetes and championed tight glycemic control (TGC), the team had ultimate accountability and responsibility for all aspects of diabetes care. Complementary knowledge and skills allowed the team to build upon each other's strengths in developing an educational program that would disseminate the requisite knowledge and training to ensure professional competency throughout the care system.

Core Competencies

Core competencies related to TGC and diabetes care include the proper use of insulin and other diabetes medications, medical nutrition therapy, point-of-care testing, hypoglycemia treatment and concomitant therapies. Educational methods to successfully promote competency include case scenarios with exercises that require critical thinking and problem-solving skills to answer the questions correctly, simulation exercises, clinical rounding on all shifts, observation and shadowing experiences and cross-discipline training. Tables 1 and 2 provide examples of insulin competencies and a question designed to promote critical thinking skills.

Assessing Level of Knowledge

Before developing a strategic plan for glycemic-management education, the team conducted a thorough assessment of each professional discipline's current knowledge and skills and reviewed and inventoried the

available tools and reference materials. At UMMC 73% of the nursing staff held a bachelor's degree or higher, whereas at a community affiliate, the overwhelming majority held an associate's degree. Knowing the staff's training and educational background, particularly with regard to critical thinking skills and clinical judgment, was essential to determining the appropriate educational content and teaching methods.

To determine the current knowledge level of the staff, the team developed an interdisciplinary tool that evaluated critical thinking skills related to insulin, basal/bolus insulin therapy, carbohydrates and hypoglycemia. Only 44% of the staff achieved a passing score of 90%. Education was needed to ensure competency before any new protocols, order sets and practices could be implemented.

Development of a Strategic Plan for Education

The challenge of providing education to 1,800 staff nurses with varied work schedules was compounded by budget constraints related to "non-productive" education time and the administration's need to understand and support the need for this training. Another challenge was "information acquisition fatigue"—the constant introduction of new information, equipment, processes and change that leads to an inability to process and internalize the information. Based on the assessment of knowledge, a plan for edu-

cation was developed that included critical information and core competencies, categorized as "must know" and "nice to know" information, and evaluated learning outcomes.

The educational plan for diabetes management and TGC initiatives included employee orientation, tests of medication knowledge, preceptor guidelines and curriculum, annual competency testing for each discipline (physician, nurse, dietitian and pharmacist), professional development and continuing education, and resource or remedial support. For facilities affiliated with an academic health center, the plan also included a review of the School of Nursing's curriculum and development of strong graduate student preceptorships.

Central nursing's new employee orientation was a perfect opportunity to impart the necessary knowledge and understanding of glycemic management. A review of diabetes classifications, insulin basal-bolus management, the rationale for TGC, acute-care glycemic targets and nutrition therapy with consistent carbohydrates established the standard of practice for nurses entering the institution. By incorporating relevant diabetes scenarios on the new employees' test, their level of knowledge could be assessed before they left formal orientation. Preceptors on nursing units also had their knowledge validated before they modeled diabetes care for new staff.

Professional Development

After competency was achieved, the next stage was continuing education on the basics of diabetes management, special-population needs, research and advanced practice taught across the continuum of care. Methods to facilitate learning included the development and use of case studies and case scenarios, grand round presentations, web-based learning modules, journal clubs, resource toolkits for each patient care unit, medication charts, pocket cards and staff participation in presentations. A creative and innovative approach to education was welcomed by staff and has proven more effective for sustained professional growth.

Summary

Lessons learned from a successful inpatient glycemic management improvement program suggest that the following can help ensure professional competency in diabetes management to improve quality outcome measures, enhance customer satisfaction and increase staff retention:

- Establish an interdisciplinary Acute Care Diabetes Advisory Committee.
- Identify core competencies related to diabetes management and TGC.
- Assess staff's current level of knowledge.
- Ensure that the administration understands and supports the concept of training to assure competency.
- Develop a plan for education that includes critical information and core competencies, differentiates between "must know" and "nice to know" information and evaluates learning outcomes.
- Develop an educational program that includes employee orientation, medication-knowledge tests, preceptor guidelines and curriculum, annual competency testing, continuing education, resource or remedial support and, where applicable, a

Table 1. Core Competencies for Insulin

- Types, actions, peaks, duration of insulins
- Intravenous insulin
- Basal-bolus subcutaneous insulin management
- Insulin storage and administration
- Skills-utilization of pens, devices, vials and syringes
- Carbohydrate counting with prandial bolus
- Correction scale insulin
- Hypoglycemia prevention

School of Nursing curriculum review and strong graduate student preceptorships.

- Use creative and innovative approaches for continuing education on the basics of diabetes management, special-population needs, research and advanced practice across the continuum of care.

Table 2. Example of Competency Questions

- JP is a 58-year-old male with Type 2 DM S/P a right knee replacement. JP is one day post-op and has experienced some nausea through the night. JP did not receive his NPH insulin last evening because he had been NPO. This morning, his blood glucose pre-breakfast is 388 mg/dL. JP's orders include:
 - Clear liquid diet
 - Low consistent carbohydrate (1200-1500 calories, 3 CHO units per meal)
 - Glucose monitoring ac meals and HS
 - NPH insulin 22 units daily at 2000
 - Aspart insulin prandial bolus-fixed; 3 units aspart subcutaneously per meal
 - Aspart insulin correction bolus with each meal based on pre-meal blood glucose:
 - BG 120-149 mg/dL give 2 units Aspart SC
 - BG 150-199 mg/dL give 3 units Aspart SC
 - BG 200-249 mg/dL give 4 units Aspart SC
 - BG 250-299 mg/dL give 7 units Aspart SC
 - BG 300-349 mg/dL give 10 units Aspart SC
 - BG > 350 mg/dL give 12 units Aspart SC

Questions:

- Plan a 3 CHO clear liquid breakfast tray for JP.
- How much aspart insulin will JP receive this morning?
- When will the aspart be administered?
- Should JP have received his NPH last evening?

BG = Blood glucose

Applying Glucometrics to Tight Glycemic Control

Jacqueline Thompson, MAS, RN, CDE, Director, Diabetes Service Line,
Sharp Healthcare, San Diego, CA

Key points

- "Glucometrics" is the assessment of glucose control that includes four measures: glycemic levels, efficacy of control, rate of adverse events and the impact on clinical outcomes.
- Our goal was to improve glycemic control without increasing the risk of hypoglycemia.
- At baseline 33% of patients had poor glucose control, defined as at least one daily episode where blood glucose < 65 mg/dL or > 200 mg/dL, and 18.2% experienced extreme blood glucose excursions (> 300mg/dL).
- Glucometrics were developed for patients in the intensive care unit (ICU). Extreme values were modified to blood glucose > 180 mg/dL or < 50mg/dL.
- Results were shared on a monthly basis at all levels of the organization.
- From 2002 to 2006, a 30% reduction in out-of-control days was realized, suggesting that the use of Glucometrics can help improve clinical performance and patient outcomes.

Although glycemic target ranges have been recommended for hospitalized acute- and intensive-care patients, no consensus exists as to how a single hospital or hospital system can gauge its clinical performance compared to others. "Glucometrics" is a way of assessing glucose control that includes four measures: glycemic levels, efficacy of control, rate of adverse events and the impact on clinical outcomes.

At Sharp, we initially set out to improve the glycemic control of patients with a secondary diagnosis of diabetes without increasing the risk for hypoglycemic events—the concern most frequently expressed by our medical staff with regard to achieving improved glycemic control. To determine our baseline for glycemic control, all laboratory

and point-of-care (POC) blood glucose data were obtained from Sharp's clinical information system for calendar year 2002. Patients were identified by DRG 250, which is a secondary diagnosis of diabetes. We included all laboratory and bedside blood glucose values and double-checked all glucose levels >600 mg/dL for coding error or missed diagnosis. It was found that 33% of patients had poor control, defined as at least one episode where blood glucose was < 65 mg/dL or > 200 mg/dL. It was also noted that 18.2% experienced extreme blood glucose excursions, which was defined as blood glucose > 300 mg/dL.

Sharp refined its Glucometrics for the acute-care setting to include a "Well-managed Day" (adequately monitored and not out of control), added statistical analy-

sis of the data including mean and standard deviation and reported "extreme" data (blood glucose < 60 and > 300 mg/dL). Glucometrics were developed for use with all patients admitted to the intensive care unit (ICU) that show the distribution of blood glucose levels. Extreme values have been modified to blood glucose > 180 mg/dL or < 50 mg/dL.

Results were shared each month at all levels of the organization from executive leadership, who receive a report summarizing all Sharp hospitals, to individual hospitals, which receive results benchmarked against all other hospitals within Sharp, and to individual patient care units. More information can be obtained from the data-rich repository to evaluate population subsets such as trauma, cardiac and renal transplant patients or physicians and medical groups.

During the four-year period from 2002 to 2006, a 30% reduction in out-of-control days has been realized from using Glucometrics to evaluate glucose management of inpatients. This suggests that providing timely and accurate clinical performance data to frontline clinical teams can help improve clinical performance and patient outcomes.

Intensive Insulin Therapy for Tight Glycemic Control

Philip J. Schneider, MS, FASHP

Editor

The value of a conference of this type is not only the outstanding information presented in the lectures, but also discussing the application of this information among the distinguished presenters and invited guests. While consensus seems to be emerging among experts in this field, much still needs to be done to reach agreement on issues like the impact on hospital costs, a reasonable target for treatment outcome, methods, the administrative aspects needed to achieve tight glycemic control, the risks and consequences of hypoglycemia and the best method to measure blood glucose. What follows are some of the comments from the discussions at this roundtable about these six topics. Participants shared their insights about how intensive insulin therapy might actually be used to achieve tight glycemic control and debated issues where consensus has yet to be reached.

What is the impact of intensive insulin therapy (IIT) on hospital costs?

My administrative colleagues will ask, “What is this going to cost? What’s the upfront cost?” I’m not talking about hospital length of stay reductions and all those other important things, because the administrators, at least at my institution, don’t seem to be particularly fazed or impressed by those data. They want to know, “How much is this machine or device or computer going to cost me? What’s the capital investment up front?” I need that answer if I’m going to convince them to buy. Otherwise they’re going to say, “Sorry, too much money.”

John P. Kress, MD

I’d be happy to answer “What is this going to cost?” One ventilator-associated pneumonia for you...for the whole hospital.

W. Patrick Burgess, MD, PhD

IIT might be time-saving, because if you achieve tight glycemic control, you can avoid 40% of acute renal failures and

the need to start hemodialysis or hemofiltration. You can get your patient off of the ventilator more quickly. It might even save time if you have a good protocol and also if you could work with continuous monitoring.

Christophe De Block, MD

We were interested in implementing continuous monitoring for tight glyce-mic control at our hospital, so I did look into the cost. I was quoted a cost of \$5 per day/per bed. The cost is not based on whether your patient is using the device, it’s based on the cost of your beds.

Jacqueline Thompson, MAS, RN, CDE

We looked into that, too. The server alone was \$12,000, and then we looked at the cost per ICU bed. For our institu-tion, the cost was about \$50,000.

Kris Hedges, MBA

The savings is on the order of \$20 to \$30 per bed, when you look at the reduc-tion in the number of infections and length of stay.

W. Patrick Burgess, MD, PhD

What is a reasonable target for blood glucose control?

The range of 80-110 mg/dL has been touted as a goal, but if you look at the clinical experience to date, patients are not in that range for very long—in some cases less than half the time, or perhaps 40%.

Guy Soo Hoo, MD

If patients don’t have diabetes, our glycemic range is about 80-130 mg/L; 80 fasting and maximum 130. We think patients shouldn’t be outside the nor-mal range of blood glucose variation that non-diabetics have within a 24-hour period.

Kalman Holdy, MD

There is huge inter-patient variation in how people respond. When a patient is really sick, blood sugar varies enor-mously.

Simon Finfer, MB, BS, FRCP, FRCA, FJFICM

We have a commercially available computerized program for insulin infu-sion dosing and keep our patients at goal about 60% of the time. We get our patients to goal in about six hours at 80-110 mg/dL.

Judith Jacobi, PharmD, FCCM, FCCP, BCPS

What factors complicate glycemic control in critically ill patients?

One factor is how the pharmacy prepares a product. If the insulin infusion is always mixed in 5% dextrose, a 50-mL bag of 5% dextrose isn't going to make a big difference. But how many patients also get antibiotics or other medications that are provided in dextrose-based solutions?

Judith Jacobi, PharmD, FCCM, FCCP, BCPS

Another factor is stopping TPN immediately. You can't adjust for that.

Bruce W. Bode, MD

Steroids certainly are a big question with hyperglycemia that we encounter in most of our patients in the ICUs. Generally the steroids are given as bolus doses in the ICU. There's a lag between the time the steroids are administered, and a different lag in terms of insulin coverage.

Kalman Holdy, MD

We start with a somewhat higher target blood glucose range of 80-150 mg/dL. By starting with a higher target range and mixing intermittent medications, such as antibiotics, in normal saline, and

by standardizing the site where blood for glucose testing is obtained, we were able to obtain the goal of 80-150 mg/dL in 80% of tested blood glucose values, with a hypoglycemia rate, i.e., blood glucose < 40 mg/dL, less than 1%.

Rhonda S. Rea, PharmD

The glycemic control diet is really based on the source of hyperglycemia in the majority of patients who are ill. In the majority of cases, the reason that patients are hyperglycemic is not exogenous nutrition or glucose; it is endogenous production of glucose in the liver.

Kalman Holdy, MD

What are the administrative aspects of an IIT program?

Right now with our computerized system, every nurse is trained in a 15-minute segment upon enrollment in the hospital. All our glucoses are done by medical assistants or medical techs. Except in the ICU on a one-to-one ratio, the nurse still is very much involved in it. There's really almost no time involved except to set up the device, which takes about three minutes. So the true nursing time is very

minor; it's not two to three hours a day per patient at all. A lot of the work is done by nursing partners, so the time to do a glucose, get it back to the nurse and input it would be probably three to five minutes.

Bruce W. Bode, MD

We have a training tape on the web that teaches the nurses how to use bedside testing, so that an institution can train their new nurses by using the web-based tutorials. We find that programming the time into the software that about 40% of the time, the Accu-Cheks are every two hours. This reduces 40% of the fixed cost of the disposables from the point-of-care device because of less frequent testing. That also saves the five minutes times the 40%. We find that on average, somewhere between 14 and 16 checks a day will keep a patient in control.

The decision-making takes somewhere between 10 and 15 seconds. The nurse walks up to a computer and walks away with an answer. It's a few keystrokes and they get used to doing it. The fewer keystrokes they use, the faster they get.

W. Patrick Burgess, MD, PhD

The treatment of hypoglycemia is extremely labor-intensive—with repeating glucoses every 15-20 minutes and then implementing whatever intervention is called for per your protocol.

R. Daniel Pollom, MD

We have a shortage of nurses. We're using 600 registry, or travel nurses in our facilities and retraining isn't going to help us. We instituted a policy so that if there is a low blood glucose reading and the nurse does not validate it and ask whether the patient really looks hypoglycemic, another nurse has to perform a double-check.

Jacqueline Thompson, MAS, RN, CDE

What is the risk of hypoglycemia with IIT?

The hypoglycemic rate using a computer, EndoTool™ or Glucomander®, to calculate the infusion rate is less than 1%, not only in the institutions where they were promoted and designed but also in other institutions. In the NICE-SUGAR trial, the hypoglycemia rate is 5%. Why would there be a difference in the rates of hypoglycemia?

Chris Hogness, MD, MPH

I believe a fair number of low glucose levels are not actually hypoglycemic events, because when the glucometer reading is checked against the lab results, a high proportion of the glucometers are under-reading. But the majority of the glucometer readings are not being checked.

Simon Finfer, MB, BS, FRCP, FRCA, FJFICM

Hospital meters err on the side of being lower than laboratory values as a protective mechanism. That's why, when you send your data to the lab, very few of the readings were truly less than 40; they were trending towards 60 but trending toward the low range.

Bruce W. Bode, MD

The hypoglycemia risk does seem higher in that setting, if you're not giving some basal glucose.

Judith Jacobi, PharmD, FCCM, FCCP, BCPS

The gold standard test of pituitary function is an insulin tolerance test. And the goal sugar is below 40 mg/dL. It's a diagnostic test to produce a pituitary response, and the goal is to get the blood sugar transiently below 40. There's a large body of experience over 30 years with that particular test showing no adverse effects from transient hypoglycemia.

Robert Osburne, MD

We also have to take into account the duration of the hypoglycemia. If you measure glycemia on a continuous basis, see it drop off to below 40, and correct it immediately, there would probably not be a problem. But if you don't monitor glycemia continuously or frequently and your patient stays below 40 for more than 30 minutes, then you have a problem.

Christophe De Block, MD

We are currently doing a study in older type 2 diabetics with pacemakers, and taking them from 150 mg/dL down to 50 at a certain rate, then taking them back up to 150 and down to 50 at a faster rate, and people develop pretty significant CNS symptoms between 60 and 65. When you get them down to 50, they often stop talking and they're "spacey." We leave them at 50 for about half an hour, and we're looking to see if the EKG changes.

The real issue is permanent injury, and that's fairly rare.

Jeffrey I. Joseph, DO

It would be a real shame if people went away from this conference thinking that there was any credible evidence at all that one blood glucose of less than 40 was harmful. Because I don't believe there is any credible evidence.

Simon Finfer, MB, BS, FRCP, FRCA, FJFICM

What is the best way to measure blood glucose concentrations for IIT?

I think the quality of the technology at the bedside for measuring glucose is a really important point. At our unit, we noticed that we had a 20% to 30% difference between our glucometer results and laboratory values.

The glucometers were telling us that the patient's values were fine, when in fact the patient was hypoglycemic. We did a quality analysis and realized that, at least in our population, the major reason for the error was a high prevalence of anemia in our patients.

We tested four different glucometers, and all of them had an approximately 20% error rate. The manufacturer tells us, "Well, 15% is okay." That was true back in the era of trying to keep diabetics < 200mg/dL, but when you're trying to

keep someone between 80 to 110 mg/dL, you need to know that your measurement is accurate. Checking glucometers against laboratory reference values is very important, because glucometers are subject to a lot of error.

Heather Pidcoke, MD

We had an issue with the glucometers at our hospital as well; we were getting some erroneous readings. And when we investigated it further, the blame was placed on nursing, as if their technique were inappropriate. But the truth was that if an adequate blood sample wasn't applied, if it didn't wick completely and cover the yellow area completely, the meter was capable of giving an erroneous reading by 54%, high or low.

Jacqueline Thompson, MAS, RN, CDE

I've heard a lot of criticism of the meters, but we often will do a sample in duplicate or triplicate with the same meter and have a fairly small standard deviation. The bigger issue is getting a quality sample. The size of the drop on the fingerstick is an issue, I agree, but we actually had the smaller standard deviation from the fingersticks.

If a patient is in shock and has low blood pressure and cold hands, that's an

issue. If you're squeezing the blood, that does alter the measurement. However, I'm finding much more of an issue from sampling from a radial arterial line or a venous line. Everybody does it a little differently. One, there's a lot of phlebotomy involved, and two, if there's even a little bit of residual in the stopcock or variation in how you're doing it, this can result in a low or high dilutional error.

Jeffrey I. Joseph, DO

Regarding the continuous glucose monitoring, I'm sure when we have results real-time and on a computer screen, it will help. But another huge advantage is that we can pull so much data out of these devices — areas under the curve, percentage of time in certain glycemic ranges and indexes of variability.

Christophe De Block, MD

When I tested our glucometers, I lined up five and did them all at the same time. They're very consistent with each other. The problem is they're precise but not accurate. When I would send the sample off to the lab, the glucometer results all showed the same amount of difference from the lab value.

Heather Pidcoke, MD

Table. Major Published Randomized Controlled Trials with Insulin Therapy in Critically Ill Patients

From: Pittas AG. Meta-analysis of Randomized Trials of Tight Glycemic Control (on pg 21)

	Population	Insulin-based Intervention	Glucose Goal (mg/dL)	N	Outcomes
Malmberg, 1995 (DIGAMI)	Diabetes and Acute Myocardial Infarction	Intensive Acute and Intensive Long-term Therapy vs. Routine Therapy	126 – 180 None	306 314	No difference between groups in: Acute (in-hospital) mortality Reduction with Intensive Therapy in: Long-term (outpatient) mortality, 26%
Van den Berghe, 2001	Adult Surgical ICU (63% cardiac surgery patients)	Intensive IV Therapy vs. Routine Therapy	80 – 110 180 – 200	765 783	In-hospital reductions with Intensive Therapy in: Mortality, 34% Blood-borne infections, 46% Acute renal failure, 41% Transfusions, 50% Critical illness polyneuropathy, 44%
Malmberg, 2005 (DIGAMI 2)	Type 2 Diabetes and Acute Myocardial Infarction	Intensive Acute and Intensive Long-term Therapy vs. Intensive Acute and Routine Long-term Therapy vs. Routine Acute and Long-term Therapy	126 – 180 (Acute) 90 – 180 (Long-term) 126 – 180 (Acute) None (Long-term) None (Acute) None (Long-term)	474 473 306	No differences between groups in: Acute (in-hospital) mortality Long-term (outpatient) mortality
Mehta, 2005 (CREATE-ECLA)	Acute Myocardial Infarction	Glucose-Insulin-Potassium (GIK) IV infusion x 24 hours vs. Routine Therapy	None None	10,110 10,091	No differences between groups in: 30-day mortality Cardiac arrest Cardiogenic shock Reinfarction Heart failure
Van den Berghe, 2006	Adult Medical ICU	Intensive IV Therapy vs. Routine Therapy	80 – 110 < 180	595 605	No differences between groups in: Acute (in-hospital) mortality In-hospital reduction with Intensive Therapy in: Patients staying in the ICU for 3 or more days In-hospital improvements with intensive therapy in: Acquired kidney disease Weaning from mechanical ventilation Hospital discharge

The CareFusion Center for Safety and Clinical Excellence Invited Conference

Intensive Insulin Therapy for Tight Glycemic Control

June 7-8, 2007

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