

A replicable method for blood glucose control in critically ill patients

Alan H. Morris, MD; James Orme Jr, MD; Jonathon D. Truweit, MD; Jay Steingrub, MD; Colin Grissom, MD; Kang H. Lee, MD; Guoliang L. Li; B. Taylor Thompson, MD; Roy Brower, MD; Mark Tidswell, MD; Gordon R. Bernard, MD; Dean Sorenson, PhD; Katherine Sward, RN, PhD; Hui Zheng, PhD; David Schoenfeld, PhD; Homer Warner, MD, PhD

Context: To ensure interpretability and replicability of clinical experiments, methods must be adequately explicit and should elicit the same decision from different clinicians who comply with the study protocol.

Objective: The objective of this study was to determine whether clinician compliance with protocol recommendations exceeds 90%.

Design: We developed an adequately explicit computerized protocol (eProtocol-insulin) for managing critically ill adult patient blood glucose. We monitored clinician compliance with eProtocol-insulin recommendations in four intensive care units in four hospitals and compared blood glucose distributions with those of a simple clinical guideline at one hospital and a paper-based protocol at another. All protocols and the guideline used intravenous insulin and 80 to 110 mg/dL (4.4–6.1 mmol/L) blood glucose targets.

Setting: The setting for this study was four academic hospital intensive care units.

Patients: This study included critically ill adults requiring intravenous insulin.

Intervention: Intervention used in this study was a bedside computerized protocol for managing blood glucose.

Main Outcome Measure: The main outcome measure was clinician compliance with eProtocol-insulin recommendations.

Results: The number of patients was 31 to 458 and the number of blood glucose measurements was 2,226 to 19,925 among the four intensive care units. Clinician compliance with eProtocol-insulin recommendations was 91% to 98%. Blood glucose distributions were similar in the four hospitals (generalized linear model $p = .18$). Compared with the simple guideline, eProtocol-insulin glucose measurements within target increased from 21% to 39%, and mean blood glucose decreased from 142 to 115 mg/dL (generalized linear model $p < .001$). Compared with the paper-based protocol, eProtocol-insulin glucose measurements within target increased from 28% to 42%, and mean blood glucose decreased from 134 to 116 mg/dL (generalized linear model $p = .001$).

Conclusions: The 91% to 98% clinician compliance indicates eProtocol-insulin is an exportable instrument that can establish a replicable experimental method for clinical trials of blood glucose management in critically ill adults. Control of blood glucose was better with eProtocol-insulin than with a simple clinical guideline or a paper-based protocol. (Crit Care Med 2008; 36:1787–1795)

KEY WORDS: Human; clinical protocols; decision support systems; clinical; research; blood glucose; insulin

Replicability is a basic requirement of science (1–7) and should be a requirement of clinical trial experiments (1, 8–12). Experimental methods that cannot

be replicated may explain inconsistent clinical trial results from the same investigators (13, 14). Without replicable methods, we cannot distinguish differences resulting from subject populations from those result-

ing from clinical trial conduct. Replicability requires detailed experimental methods. However, the methods of many clinical trial experiments are not adequately explicit. For example, recent trials of intravenous insulin for management of blood glucose in critically ill patients (13) included the following rule: “If blood glucose approaches the normal range, adjust with increments/decrements of .1 to -0.5 IU per hour” (13, 14). Thus, bedside clinician practice became part of the experimental method. Different clinicians frequently interpret and execute such protocol rules differently. Because the elements of their decision-making are not known, the clinical experimental method cannot be completely reported.

From the Pulmonary and Critical Care Divisions, Departments of Medicine (AHM, JO, CG), LDS Hospital and the University of Utah School of Medicine, Salt Lake City, UT; the University of Virginia (JDT), Charlottesville, VA; the Division of Critical Care Medicine (JS, MT), Baystate Medical Center, Springfield, MA; the National University Hospital (KHL, GLL), Singapore; the Pulmonary and Critical Care Division (BTT) and the Biostatistics Center (HZ, DS), Harvard Medical School, Boston, MA; Pulmonary and Critical Care Medicine (RB), Johns Hopkins University, Baltimore, MD; the Division of Allergy, Pulmonary, and Critical Care (GRB), Vanderbilt University, Nashville, TN; the Department of BioMedical

Informatics (DS, HW), University of Utah School of Medicine, Salt Lake City, UT; and the Department of Nursing Informatics (KS), University of Utah School of Nursing, Salt Lake City, UT.

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For information about this article, E-mail: ldamorri@ihc.com

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When methods are not adequately explicit, it is difficult or impossible to replicate the experiments, and it may be impossible to interpret a trial result. Equivalent outcomes in two study groups could be truly equivalent or be spurious as a result of clinician inconsistency in interpreting protocol rules. Confidence in an outcome requires confidence that the experimental intervention was applied as intended. If one treatment is favored but we do not know how the protocol rules were interpreted, it is difficult to use the results to modify clinical practice.

Clinical trial protocols should be adequately explicit, consistently leading to the same decision for a given set of clinical conditions (15). The protocol for an intervention must be clear, understandable, and clinically sensible. Clinicians, advocating the patients' best interests, should be free to decline protocol recommendations that do not make sense. Clinical sense and clinician acceptance are enhanced if the protocol improves intermediate clinical outcomes (for example, blood glucose concentrations).

Anticipating the need for clinical trials of blood glucose management, we designed an adequately explicit protocol for controlling blood glucose with a continuous intravenous insulin infusion. The protocol recommendations were detailed and internally valid. They did not require interpretation by bedside clinicians. Clinicians were asked to enroll a patient if he or she belonged to the clinical subset for which the protocol was developed. This protocol possesses the critical attribute of enabling consistent clinician decisions but provides the opportunity for a clinician to decline any recommendation. The protocol rules are complicated and not readily understandable in paper format because they are designed to produce recommendations for managing insulin infusions across a wide range of clinical conditions and include rules for safety and for managing hypoglycemia. We developed a computerized version that generates simple, easily understood recommendations for initiating and adjusting insulin infusions, glucose measurement frequency, and management of hypoglycemia. We assessed clinician acceptance of the computerized protocol (eProtocol-insulin) recommendations and their effect on blood glucose distributions in critically ill adults in this quality improvement study.

METHODS

The computerized protocol (eProtocol-insulin) was installed on stand-alone laptops. The laptops were distributed to clinical areas when patient care with eProtocol-insulin was started. An evaluation of the software by a group of naïve users (nursing and medical students) found the software intuitive and easy to use with virtually no training needed. At the participating intensive care unit sites, an initial group of nurses learned how to use the software. These nurses provided training, as needed, to other nurses. In addition, each laptop contained a tutorial that was available whenever the user desired. We elected to adopt the same data-recording process used for bedside paper flowsheets and similar tools. Formal documentation of the patient's state occurred in the patient medical record.

Bedside nurses entered the blood glucose value with the laptop keyboard. At LDS Hospital, the blood glucose value was automatically retrieved from the hospital electronic medical record. eProtocol-insulin acted as a calculator to compute the patient's recommended insulin dose based on an explicit set of rules (Appendix 1). We chose not to use double data entry or other data verification techniques to reduce the nurse work burden. Clicking the electronic protocol screen signified an "intent to" accept the recommendation. The nurses still needed to verify drug administration through their usual medical record documentation process. We did not attempt to confirm that the nurse actually set the intravenous pump according to the accepted recommendation. We plan to add a verification of the intravenous pump rate in our next study. We carefully considered this strategy and reviewed the pros and cons of this approach. We concluded that enabling bedside nurses to use eProtocol-insulin with minimum effort outweighed the theoretical advantages of additional security and double data entry. The bedside clinician indicated the presence or discontinuation (under 50% predicted) of nutritional intake. We defined predicted nutritional intake (see end of Appendix 1).

The bedside eProtocol-insulin laptop computer contained identifiable Health Protected Information as do all bedside records. These identifiers were limited to the patient's name or initials and dates of obtaining the insulin dose recommendation. Data were deidentified before being transferred to the coordinating center. Only the local site investigator could link the study number with the patient; these linking data were kept locally in a locked file by the local site investigator and coordinator.

We used exclusively intravenous insulin and 80 to 110 mg/dL (4.4–6.1 mmol/L) blood glucose targets for quality improvement. LDS Hospital Shock/Trauma/Respiratory Intensive

Care Unit investigators iteratively developed and refined the point-of-care eProtocol-insulin (Appendix 1) (15). eProtocol-insulin has a simple single computer screen that allowed a clinician to enter a blood glucose value. eProtocol-insulin then generated one or more individualized patient recommendations. Patient weight and the most recent blood glucose determined initial insulin infusion rate (expressed in units/kg per hr; Appendix 1). The initial algorithm was developed for a 70-kg person. The ratio (patient weight/70 kg) is the patient's normalized weight relative to a 70-kg person. Only the initial insulin infusion rate is weight-dependent. Thereafter, the insulin infusion rate is weight-independent. The current infusion rate, the difference between the most recent glucose and the target, and the rate of change of blood glucose, determined subsequent insulin infusion rates. The eProtocol-insulin bedside computer screen displayed the time remaining to the next glucose measurement, although clinical indications could prompt an earlier measurement.

We used the eProtocol-insulin for quality improvement between March 2005 and November 2006 at four hospitals. Because this was a quality improvement study, we had no control over the patient populations in the participating intensive care units. Our enrolled subject number was too small for ultimate clinical outcome assessment (for example, length of stay, survival). We only used eProtocol-insulin in patients for whom intravenous insulin had or was to be prescribed, including patients with diabetes, because eProtocol-insulin is adaptive. We did not include patients with diabetic ketoacidosis, because we had not developed rules for ketoacidosis. We did not use randomization of either patients or clinicians. eProtocol-insulin was used consistently for all enrolled patients. Blood glucose was measured by any local method with arterial, venous, or finger stick blood samples. Institutional Review Boards at all participating hospitals approved publication of these quality improvement data. We carefully considered this strategy. We elected to use whatever process was operating in the participating intensive care units, because this was a quality improvement study. Had we attempted to standardize the blood sampling site or the measurement technique, we would have disrupted the processes of care in many intensive care units. Although we recognize that differences between techniques are real and deserve consideration, we are not aware of data that inform how these differences might influence bedside clinical decisions.

Acceptability to Clinicians

We exported eProtocol-insulin from LDS Hospital (Salt Lake City, UT) to three intensive

care units that had minimal experience using electronic decision support tools: the University of Virginia Hospital Medical Intensive Care Unit (Charlottesville, VA), the Baystate Medical Center Medical/Surgical Intensive Care Unit (Springfield, MA), and the National University Hospital Medical Intensive Care Unit (Singapore). The U.S. intensive care units had previously adopted an 80 to 110 mg/dL (4.4–6.1 mmol/L) blood glucose target (13, 14, 16). The Singapore unit had previously used a 130 to 140 mg/dL blood glucose target. eProtocol-insulin generated bedside individualized patient recommendations. eProtocol-insulin acted like a set of dynamic standing orders. Bedside clinicians (primarily nurses, but also physicians) evaluated and accepted or declined each recommendation by activating check boxes on the eProtocol-insulin screen. When a clinician declined a recommendation, they recorded the reason for declining. The eProtocol-insulin laptop computer database stored the information from which clinician compliance and categorization of reason for declining were later calculated. The clinician was said to be compliant when he or she

accepted the computerized recommendation after finding it reasonable for the patient. We expected compliance with at least 90% of recommendations to represent a sufficiently high level of acceptance by clinicians. Physicians were not required to approve each recommendation.

Effect of eProtocol-insulin on Distributions of Blood Glucose

Before using eProtocol-insulin, clinicians at intensive care unit 2 determined all insulin infusion rates with a simple guideline. They initiated intravenous insulin when anticipated intensive care unit stay exceeded 48 hrs and at least two glucose values exceeded 140 mg/dL (7.8 mmol/L). Before using eProtocol-insulin, clinicians at intensive care unit 3 used a bedside paper-based protocol (Appendix 2). At each of these two sites, we compared the distribution of blood glucose measurements with either the simple guideline or the paper-based protocol to the distribution with eProtocol-insulin.

We assessed statistical significance of differences between blood glucose distributions (mean, within 80–110 mg/dL target, ≤ 40 mg/dL) using a generalized linear model (GZLM) to account for patient effect (17). For data in Table 1, we analyzed continuous variables using parametric tests and categorical variables using nonparametric tests.

RESULTS

Patient Group Characteristics

Primary diagnostic categories, mechanical ventilation, Acute Physiology and Chronic Health Evaluation II scores, intensive care unit and hospital lengths of stay, and mortality differed among the four intensive care unit computerized protocol patient groups using various tests of significance (Table 1). Results from *t*-test analyses suggest that intensive care unit and hospital lengths of stay were different between the eProtocol-insulin and guideline patients at inten-

Table 1. Demographic data

| Intensive Care Unit Intensive Care Unit Type Decision-Support Instrument | 1 Open Computer | 2 Closed | | 3 Closed | | 4 Closed Computer |
|---|-----------------------|----------------------|----------------------|-----------------------|----------------------|-------------------------|
| | | Guideline | Computer | Paper | Computer | |
| Number of patients | 458 | 74 | 31 | 255 | 38 | 228 |
| Mean age (yrs) | 55 ± 18 | 62 ± 19 | 65 ± 16 | 58 ± 16 | 57 ± 18 | 64 ± 16 |
| Male (%) | 60.9 | 58.1 | 54.8 | 50.4 | 52.6 | 57.4 |
| APACHE II ^a | 19 ± 7 | 20 ± 6 | 18 ± 6 | See CMI | 27 ± 9 | 27 ± 8 |
| Mechanical ventilation (%) ^a | 92% | 77% ^b | 100% ^b | 90% | 90% | 75% |
| Mean intensive care unit length of stay (days) ^a | 11 ± 11 | 7 ± 6 ^a | 17 ± 12 ^a | 9.4 ± 11 ^d | 17 ± 22 ^d | 4 ± 4 |
| Mean hospital length of stay (days) ^a | 16 ± 13 | 20 ± 20 ^c | 34 ± 18 ^c | 24 ± 22 ^e | 33 ± 33 ^e | 25 ± 31 |
| Died in intensive care unit (%) ^a | 9.2 ^f | 13.6 | 9.7 | 21.7 | 28.9 | 20.6 |
| Died in hospital (%) ^f | 18.3 | 20.3 | 19.4 | 31.3 | 39.5 | 28.0 |
| Primary diagnostic categories | | | | | | |
| Sepsis ^a (%) | 12 | 6.8 | 6.5 | 13.5 ^g | 34.2 ^g | 20.4 |
| Pneumonia ^a (%) | 2.6 | 8.1 | 12.9 | 4.8 | 0 | 26.8 |
| Acute respiratory failure, aspiration, pulmonary embolism, other pulmonary ^a (%) | 13.5 | 8.1 | 3.2 | 19.1 | 26.3 | 2 |
| COPD/asthma exacerbation ^a (%) | 0.4 | 1.4 | 0 | 3.9 | 2.6 | 13.6 |
| Cardiac (%) | 3.7 | 4.1 | 6.5 | 7.4 | 5.3 | 5.2 |
| Gastrointestinal (cirrhosis, liver failure, gastrointestinal bleeding) ^a (%) | 12.8 | 0.0 | 3.2 | 6.1 | 5.3 | 1.6 |
| Pancreatitis (%) | 1.1 | 4.1 | 0 | 2.6 | 2.6 | 0 |
| Renal failure ^a (%) | 1.1 | 4.1 | 6.5 | 2.2 | 0 | 7.2 |
| Poisoning (%) | 1.5 | 1.4 | 0 | 3.5 | 2.6 | 2.4 |
| Neurological (%) | 10.2 | 6.8 | 6.5 | 2.6 | 7.9 | 4 |
| Cancer (%) | 1.3 | 0.0 | 3.2 | 9.6 | 5.3 | 6.4 |
| Other medical (%) | 9.2 | 9.5 | 0 | 7.4 | 0 | 7.6 |
| Trauma ^a (%) | 22.7 | 18.1 | 22.6 | 8.7 | 2.6 | 0 |
| Postoperative ^a (%) | 7.8 | 27.8 | 29.0 | 8.7 | 5.3 | 3.2 |

Intensive care unit attributes (mean ± sd). Open, non-intensive care attending physicians can admit patients; closed, only full-time intensive care staff physicians can admit patients; COPD, chronic obstructive pulmonary disorder. ^a*p* < .0001 (Intensive care units 1–4 computerized protocol [eProtocol-insulin] patients). ^b*p* = .004. ^c*p* = .0013. ^d*p* = .0005. ^e*p* = 0.03. ^f*p* = .0011 (intensive care units 1–4 computerized protocol [eProtocol-insulin] patients). ^g*p* = .001. ^hAn additional 3.4% died in other intensive care units to which they were transferred intensive care unit-1.

Non-acute trauma and postoperative patients transferred for long-term failure to recover (e.g., prolonged mechanical ventilation). Only 36 of 38 intensive care unit-3 computerized protocol patient records were available for Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Case Mix Index at intensive care unit-3 (paper protocol patients = 6 ± 6; computerized protocol patients = 7 ± 7; *p* = .10).

Table 2. eProtocol-insulin performance data

| Intensive Care Unit | Number of Patients | Number of Glucose Values | % Clinician Compliance with | | | Mean Glucose (mg/dL) ^c | Median Glucose (mg/dL) |
|---------------------|--------------------|--------------------------|---------------------------------------|--|--|-----------------------------------|------------------------|
| | | | Computerized Protocol Recommendations | % of Glucose Values Within 80–110 (mg/dL) ^a | % of Glucose Values ≤40 (mg/dL) ^b | | |
| 1 | 458 | 19,925 | 95 | 46 | 0.10 | 113 | 105 |
| 2 | 31 | 2,846 | 91 | 39 | 0.21 | 115 | 110 |
| 3 | 38 | 2,161 | 94 | 42 | 0.19 | 117 | 106 |
| 4 | 228 | 11,290 | 98 | 41 | 0.79 | 111 | 103 |

Computerized protocol (eProtocol-insulin) performance at intensive care units 1–4. ^aGeneralized linear model $p = .0002$. ^bGeneralized linear model $p < .0001$. ^cGeneralized linear model $p = .18$.

sive care unit 2 (intensive care unit length of stay T [103] = 5.61, $p < .0001$; hospital length of stay T [100] = 3.30, $p = .0013$), and between eProtocol-insulin and paper-based protocol patients at intensive care unit 3 (intensive care unit length of stay T [266] = 3.52, $p < .0005$; hospital length of stay T [266] = 2.16, $p = .03$). At intensive care unit 2, mechanical ventilation was more common among eProtocol-insulin than guideline patients ($\chi^2 [1, n = 105] = 8.50, p = .004$). At intensive care unit 3, sepsis was more common among eProtocol-insulin than among paper-based patients ($\chi^2 [1, n = 293] = 10.22, p = .001$).

Acceptability to Clinicians

Bedside clinicians accepted 91% to 98% of eProtocol-insulin recommendations (Table 2). Clinician compliance at all sites exceeded our *a priori* 90% minimum. We categorized the 1,560 reasons bedside clinicians provided for declining 1,523 recommendations into five groups (n = number, % = % of declined recommendations):

1. Additional patient information not available to eProtocol-insulin but felt important by the bedside clinician (n = 618 [41%]). Examples include incorrect data entered in eProtocol-insulin; switched to a different tube feeding, extra insulin just given;
2. Dose disagreement (n = 448 [29%]). Examples include giving 25 rather than 50 mL of 50% dextrose in water; unable to set the insulin pump to <1 unit/hour;
3. Tactical issues (n = 125 [8%]). Examples include patient out of the intensive care unit; nurse responding to a cardiac arrest in another room;
4. Software issues (n = 85 [6%]). Examples include program not re-

sponding; count-down time inoperative; and

5. No reason given (n = 284 [19%]).

Effect of Computerized Protocol (eProtocol-insulin) on Distributions of Blood Glucose

Differences in mean glucose and percent of measurements within the 80 to 110 mg/dL target were statistically significant in the three intensive care units using three different methods to manage blood glucose (GZLM Wald $\chi^2 [2] = 229, p < .001$ for comparison of means; Fig. 1). The mean and median glucose values were lowest with eProtocol-insulin at intensive care unit 1. They were highest with the simple guideline at intensive care unit 2. The percent of glucose measurements ≤40 mg/dL was compared using generalized linear models taking into account patient effects; the difference was found to be not statistically significant (Wald $\chi^2 [2] = 5.59, p = .061$).

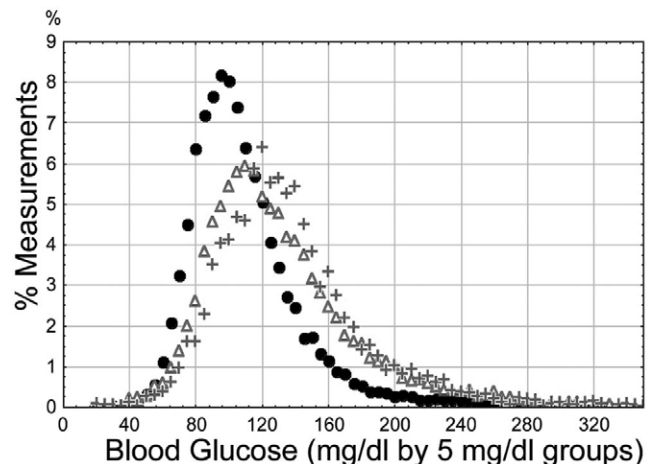


Figure 1. Blood glucose distributions in three intensive care units using three different methods to achieve blood glucose of 80 to 110 mg/dL (4.4–6.1 mmol/L). ● = computerized protocol (eProtocol-insulin) (intensive care unit 1); + = simple guideline (intensive care unit 2); Δ = bedside paper-based protocol (intensive care unit 3).

At intensive care unit 2, the distribution of blood glucose values with eProtocol-insulin was different from the distribution with the simple guideline (Figs. 1 and 2; Table 2). The mean glucose decreased from 142 mg/dL with the guideline to 115 mg/dL with eProtocol-insulin (GZLM Wald $\chi^2 [1] = 33.72, p < .001$; Table 2). The measurements within the 80 to 110 mg/dl target increased from 21% to 39% (GZLM Wald $\chi^2 [1] = 42.53, p < .001$; Table 2). The measurements ≤40 mg/dL did not change significantly (.23% to .21%, $\chi^2 [1, n = 6331] = .04, p = .85$; Table 2). The percent of patients who experienced at least one blood glucose measurement ≤40 mg/dL did not change significantly (8.1% to 9.7%, $\chi^2 [1, n = 105] = .07, p = .72$). The patients reaching the 80 to 110 mg/dL target increased from 93.2% to 100% with eProtocol-insulin (Fisher's exact test $p = .24$; Table 3). The time required for the first blood glucose measurement within 80 to 110 mg/dl decreased from 26.55 to 9.81 hrs and the number of blood glucose mea-

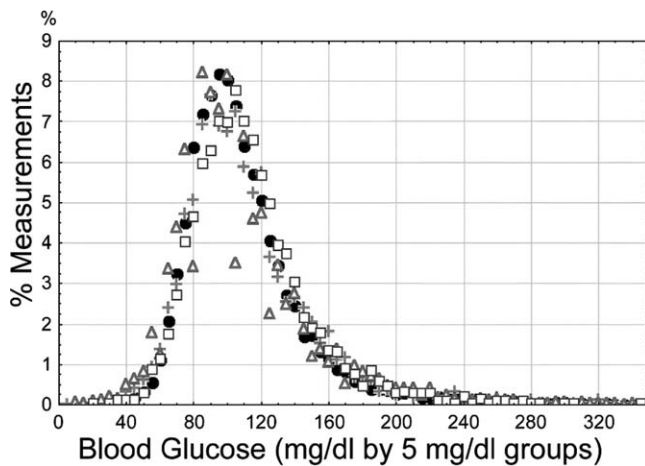


Figure 2. Distributions of blood glucose in four intensive care units using the computerized protocol (eProtocol-insulin): ● = intensive care unit 1; □ = intensive care unit 2; + = intensive care unit 3; Δ = intensive care unit-4.

Table 3. Time to first blood glucose measurement in range (80–110 mg/dL)

| Intensive Care Unit | Total Number of Patients | Patients Reaching Range (eProtocol-insulin) | | | Mean Hours to First Blood Glucose Measurement in Range | Mean Number of Blood Glucose Measurements to First Blood Glucose Measurement in Range |
|---------------------|--------------------------|---|------------------|-------------------|--|---|
| | | Number of Patients | % Total Patients | % Total Patients | | |
| 1 | 458 | 429 | 93.7 | 9.49 | 4.57 | |
| 2 | 31 | 31 | 100 | 9.81 ^a | 4.5 | |
| 3 | 38 | 35 | 92.1 | 9.24 ^a | 5.3 | |
| 4 | 228 | 212 | 93 | 8.5 | 4.22 | |

| Intensive Care Unit | Total Number of Patients | Patients Reaching Range (usual care) | | | Mean Hours to First Blood Glucose Measurement in Range | Mean Number of Blood Glucose Measurements to First Blood Glucose Measurement in Range |
|---------------------|--------------------------|--------------------------------------|------------------|--------------------|--|---|
| | | Number of Patients | % Total Patients | % Total Patients | | |
| 2 | 74 | 69 | 93.2 | 26.55 ^a | 8.39 | |
| 3 | 255 | 223 | 87.5 | 18.54 ^a | 8.08 | |

Number and percent of patients reaching the blood glucose target range (80–110 mg/dL). The mean time (hrs) and number of blood glucose measurements required for the first blood glucose measurement within range for eProtocol-insulin and for usual care (usual care data available only for intensive care units 2 and 3). The number of blood glucose measurement for eProtocol-insulin is equivalent to the number of eProtocol-insulin iterations, or runs. ^a*p* value from log-rank test is .0009.

measurements decreased from 8.39 to 4.5 with eProtocol-insulin (log-rank χ^2 [1] = 11.06, *p* = .0009; Table 3).

After introduction of eProtocol-insulin to intensive care unit 3, clinicians continued to use the paper-based protocol in some patients, whereas eProtocol-insulin was used in others. The distribution of blood glucose values with eProtocol-insulin was different from the distribution with the paper-based protocol (Figs. 1 and 2). The mean glucose decreased from 134 mg/dL with the paper-based protocol to 116 mg/dL with eProtocol-

insulin (GZLM Wald χ^2 [1] = 42.14, *p* < .001). The measurements within the 80 to 110 mg/dL target increased from 28% to 42% (GZLM Wald χ^2 [1] = 37.86, *p* < .001; Table 2). The measurements \leq 40 mg/dL did not change significantly (.07% to .18 %, χ^2 [1, *n* = 23,849] = 3.00, *p* = .08; Table 2). The percent of patients who experienced at least one blood glucose measurement \leq 40 mg/dL did not change significantly (5.1% to 11.1%, χ^2 [1, *n* = 290] = 2.05, *p* = .24). The time required for the first blood glucose measurement within 80 to 110 mg/dL de-

creased from 18.54 to 9.24 hrs and the number of blood glucose measurements decreased from 8.08 to 5.3 with eProtocol-insulin (log-rank χ^2 [1] = 11.03, *p* = .0009; Table 3).

Blood glucose distributions with eProtocol-insulin at the four intensive care units were similar (Table 2; Fig. 2). The mean values were not significantly different (GZLM Wald χ^2 [3] = 4.86, *p* = .18). However, the percent of measurements within target (80–110 mg/dL, GZLM Wald χ^2 [3] = 19.98, *p* = .0002) and \leq 40 mg/dL (GZLM Wald χ^2 [3] = 46.36, *p* < .0001) were significantly different. No clinician reported harmful consequences of hypoglycemia.

The mean times to the first blood glucose measurement within target (80–110 mg/dL) were 9.8, 9.5, 8.5, and 9.2 hrs for the four intensive care unit sites. The mean numbers of protocol iterations to the first blood glucose measurement within target (80–110 mg/dL) were 4.5, 4.6, 4.2, and 5.3 for the four intensive care unit sites.

DISCUSSION

Bedside clinicians accepted 91% to 98% of the recommendations generated by eProtocol-insulin. This clinician compliance is higher than most published protocol compliance rates (18–32). This is notable because our study sites include different patient populations (Table 1) in four different intensive care units in four hospitals and two different cultural environments (the United States and Singapore).

When we used eProtocol-insulin in intensive care units that had previously used other methods (Fig. 1), major glucose distribution differences disappeared (Table 2; Fig. 2). These results indicate that methodologic differences among the paper-based protocol, the simple guideline, and eProtocol-insulin were likely responsible for the different blood glucose distributions, not differences in patients. There were differences in the patients at these hospitals (Table 1), but eProtocol-insulin adapted to these patients' individual needs, resulting in similar distributions of blood glucose values. The increased frequency of mechanical ventilation and sepsis, at intensive care units 2 and 3, respectively, may itself account for the increased lengths of stay of their eProtocol-insulin patients.

The baseline differences in blood glucose distributions with eProtocol-insulin, the simple guideline, and the paper protocol (Fig. 1) suggest an explanation for the inconsistent results from clinical trials of interventions intended to modify blood glucose (13, 14, 33–36). We cannot be confident the different studies tested the same intervention because of differences in methods of blood glucose management (34, 36). A reduction in morbidity and mortality in mainly postoperative cardiac patients (13) was not duplicated by the same investigators in medical patients (14). Was this the result of differences inpatient populations, methodology, or simply chance? Because the methods were inadequately explicit and the experiments not replicable, we are left without an answer.

eProtocol-insulin seemed to be more effective for achieving clinician blood glucose and safety goals at intensive care units 2 and 3 than were the methods they previously used (blood glucose values were more frequently within target and mean blood glucose values decreased closer to the normal range with eProtocol-insulin; Table 2). With eProtocol-insulin, 9.4% of patients sustained at least one blood glucose measurement ≤ 40 mg/dL. This is higher than some (13) and lower than other reports (14, 37). We expect more hypoglycemic events when clinicians target lower blood glucose levels such as 80 to 110 mg/dL. Because eProtocol-insulin captures every blood glucose measurement, it can detect more blood glucose values ≤ 40 mg/dL than research methods that sample only some glucose measurements (13, 14). We have not addressed clinical outcomes. Our focus, in this quality improvement study, was the development and distribution of a method that allows replication of blood glucose management.

It is important to distinguish the replicability of eProtocol-insulin (reflected by clinician compliance with its recommendations) from its efficacy (reflected by the percent of measurements within the target) and from its safety (reflected by percent of measurements ≤ 40 mg/dL). eProtocol-insulin only standardizes clinician decisions. Because patients retain unique individual responses, one cannot expect all measurements of blood glucose to fall within the 80 to 110 mg/dL (4.4–6.1 mmol/L) target range. With the current eProtocol-insulin rules and 91%

to 98% clinician compliance, 39% to 46% of blood glucose measurements were within the target (Table 2). Some of this variation may be explained by the differences between the four intensive care unit populations (Table 1). We believe the interactions between the patient and the clinicians likely explain why we do not achieve 100% of measurements in the target range. eProtocol-insulin contains rules that model only the bedside clinical decision-maker. We did not include rules that formally and directly modeled the patient (for example, physiological models of glucose response to insulin, time constants, insulin sensitivity). We did include a rule that responded to the rate of change of blood glucose and this indirectly reflected some patient physiological characteristics. The blood glucose ultimately depends on both the clinical decision-maker and on the patient and on the interactions between decision-maker and patient. We plan to add a formal model of the patient to our protocol in the future.

Our study results are limited by the observational quality improvement method we used. This is less powerful than a formal experimental design. We also ignored the time at which clinicians accepted eProtocol-insulin recommendations when calculating clinician compliance. The significance of early or late measurements of blood glucose, relative to eProtocol-insulin recommendations regarding next assessment time, is difficult to assess.

Most guidelines and protocols require clinicians to make protocol decisions within clinical practice ranges. Clinicians make different decisions because of differences in training, experience, environmental constraints, judgment, and personality. In contrast, our adequately explicit eProtocol-insulin contains enough detail to elicit the same clinical decision from different clinicians for the same clinical data. eProtocol-insulin is sufficiently detailed to adapt to different patients' specific needs. It can deliver individualized therapy (15, 38). The similar distributions of blood glucose measurements at the four sites (Fig. 2) demonstrate that eProtocol-insulin is an exportable method. We think it could be used to conduct rigorous and replicable clinical experiments (15, 38) and could also be used directly in usual clinical care, thus translating research results into practice. This contrasts with the lack of

consensus and wide variation in practice reflected in a recent review of 12 different glucose management protocols (39).

We believe the implications of this adequately explicit method approach extend beyond the critical care research setting. It has clear application in many clinical care domains (for example, outpatient heart failure, management of infections, outpatient blood sugar control, and inpatient management of many clinical problems, including usual care of blood glucose in the seriously ill patient).

CONCLUSION

Clinicians accepted 91% to 98% of eProtocol-insulin recommendations for managing blood glucose. Clinicians were more successful achieving their blood glucose objectives with eProtocol-insulin than with a paper-based protocol or with a simple guideline. eProtocol-insulin is an exportable, adequately explicit computerized protocol that can establish a replicable experimental method for clinical trials.

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APPENDIX 1

Computerized Protocol (eProtocol-insulin) for Insulin Dosing and Glucose Control: Version 4

Goals. The computerized protocol is designed to maintain blood glucose concentration at a goal or target value. For example, the default target value for computerized protocol is 95 mg/dL. This value is in the middle of the target range, which is 80 to 110 mg/dL or 4.4 to 6.1 mmol/L. The computerized protocol allows the physician to select a range and thus a target value other than the default. For this trial, clinicians have chosen to use a common target range of 80 to 110 mg/dL (4.4–6.1 mmol/L).

Definition of Terms. δ = measured glucose – target value.

Interval = time period between glucose checks.

Desired rate of change = the rate of decrease in blood glucose that computerized protocol will consider appropriate. If the current rate of change is greater (more negative) than the desired rate of change, the computerized protocol gives a recommendation to decrease the insulin infusion rate. If the current rate of change is smaller (less negative) than the desired rate of change or if the rate of change is positive (rising blood glucose concentration), the computerized protocol provides a recommendation to increase the insulin infusion rate. The desired rate of change decreases as the blood glucose concentration approaches the target value. This concept is used to modify the insulin drip changes depending on the most recent rate of change as well as the most recent value of the blood glucose.

Mitigating factor (MF) – a factor that adjusts the desired rate of change based on δ (see subsequent equation).

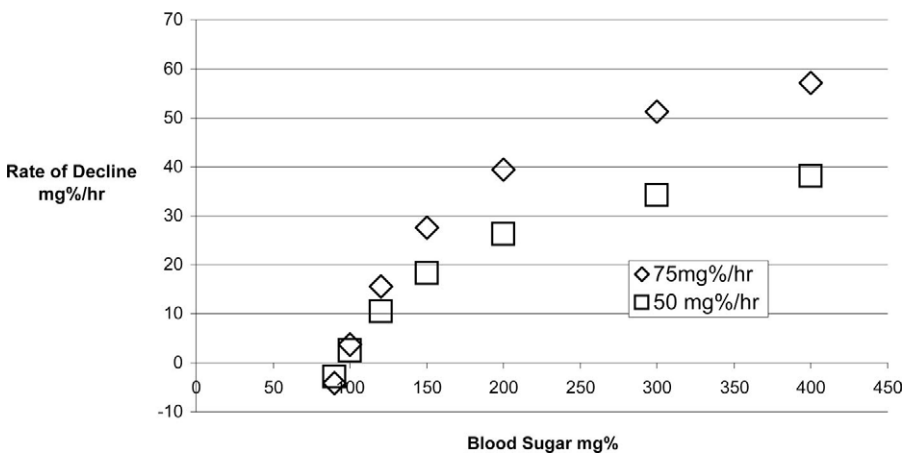
Range – The range of blood glucose values that are considered acceptable. The computerized protocol default range is 80 to 110 mg/dL (4.4–6.1 mmol/L). The range is adjustable and may be changed according to patient and study needs.

Overview. Measured glucose values are classified as above range, in range, or below range.

The computerized protocol has a specific target blood glucose value, which is in the middle of the acceptable range. The initial insulin infusion rate

depends on the initial measured glucose and the patient's weight in kilograms. Thus, a 100-kg person will start at twice the rate (units/hr) of a 50-kg person for a given blood glucose concentration. If the insulin infusion rate is >0, the subsequent changes do not reuse weight adjustment. Subsequent recommendations to adjust the insulin infusion rate depend on the current infusion rate, the most recent measured blood glucose, and the rate of change of the measured glucose over the last two measurements.

There is a maximum desired rate of change in blood glucose concentration. As blood glucose concentration approaches the target glucose concentration, the desired rate of change decreases. The subsequent graph shows how the desired rate of change varies with current blood glucose concentration for two different maximum rates of change (-50 mg/dL/hr and -75 mg/dL/hr). The maximum desired rate of change for computerized protocol is -50 mg/dL/hr.



Most paper protocols adjust insulin infusion rates in absolute unit increases or decreases to the existing rate. A disadvantage of this approach is that when the current insulin infusion rate is low, the magnitude of the rate increase (or decrease) may be relatively large. An alternative approach is to adjust the insulin infusion as a percent of the current rate. With the latter approach, insulin infusion rate is adjusted by the same proportion (%) regardless of current infusion rate. The magnitude of the adjustment depends on the current rate and the percent change. This will result in increases (or decreases) that are large when the current infusion rate is high, and this could cause wide fluctuations

in rate of change and in blood glucose concentration. To modulate this effect, the computerized protocol divides the computation by the square root of the current insulin infusion rate. This makes changes at higher infusion rates more like absolute unit changes and changes at lower infusion rates more like percent changes. For example: compare a drip rate of 1 unit/hr versus 10 units/hr. If the computation calls for a 50% increase, dividing by the square root of the drip rate will give a .5-unit increase at 1 unit/hr and a 1.6-unit increase at 10 units/hr.

Insulin infusion recommendations are given in units/hr for adults.

Computerized Protocol, Version 4: Specifics

Initial Insulin Infusion Rates for Blood Glucose >110 mg/dL (6.1 mmol/L). The computerized protocol uses .012 as the starting coefficient.

Initial insulin infusion rate = .012 × measured glucose × patient wt/70.

Infusion rate never <.5 units/hr (adult).

All recommendations rounded to the tenth of a unit/hr.

Adjustment of insulin infusion for blood glucose ≥60 mg/dL.

New infusion rate = current rate * (1 + the equation).

$$\frac{[(dg/dt - \text{desired rate of change}) / |\text{desired rate of change}|] \times |MF|}{\text{SqRoot of current insulin infusion rate}}$$

Where: dg/dt is the difference between the current value (g_2) and the preceding glucose value (g_1) adjusted to the rate of change per 1 hr.

desired rate of change = $(g_2 - g_{\text{midpoint}}) / g_2 * (-50)$.

$$MF = (g_2 - g_{\text{midpoint}}) / g_2.$$

g_{midpoint} is the target value. It is the midpoint of the target range (95 for 80-110). If $g_2 = g_{\text{midpoint}}$, then $g_2 = 1 + g_{\text{midpoint}}$ to allow solution of the new rate computation previously stated.

Sq Root = square root.

If the equation ≤(-1), then new drip rate = 0.

Adjustment of Insulin Infusion if Blood Glucose is 41 to 60 mg/dL. Discontinue insulin infusion and give .25 g/kg intravenous dextrose.

Recommendations in grams dextrose per kilogram body weight.

Adjustment of Insulin Infusion if Blood Glucose ≤40 mg/dL. Discontinue insulin infusion and give .50 g/kg intravenous dextrose.

Recommendations in grams dextrose per kilogram.

Frequency of Blood Glucose Checks. Above range: every 2 hrs.

In range: every 2 hrs. If three consecutive blood glucose values are in range, then every 4 hrs.

Below range: If blood glucose concentration <80 mg/dL, then every 1 hr.

If blood glucose decreasing rapidly and approaching target range:

If $g_2 < 140$ mg/dL and dg/dt more rapid than -20 mg/dL/hr, then every 1 hr.

Feeding. If enteral feeding or intravenous glucose administration (including total parenteral nutrition) is stopped for more than 30 mins, stop insulin drip.

Check glucose in 1 hr and restart the computerized protocol.

Feeding defined as:

D5W ≥100 mL/hr or

Enteral feeding ≥50% of goal or.

Total parenteral nutrition ≥50% of goal.

APPENDIX 2

Paper-based Protocol: Adult Critical Care Insulin Infusion Protocol

Patient Selection Criteria. Single result blood glucose >120 mg/dL (recheck blood glucose immediately before starting infusion).

MD Preparation for Insulin Infusion. Discontinue previous insulin orders.

Discontinue oral diabetes agents.

Insulin Infusion Set-up. Immediately before starting insulin infusion, obtain initial blood glucose using bedside meter.

Use only pharmacy-prepared insulin infusion. Standard insulin concentration

is 250 mL. Regular insulin in 250 mL NS (1 unit: 1 mL concentration).

Flush intravenous line with 25 mL of insulin solution before connecting infusion to patient. Piggyback insulin infusion into a dedicated maintenance intravenous.

Start insulin infusion rate as follows:

Half unit per hour for patients under 70 kg or for patients previously diet controlled, taking oral diabetes agents, or taking 30 units or less of insulin a day.

One unit per hour for patients over 70 kg or taking more than 30 units of insulin a day.

MD advice: Consider 3 to 5 units per hour initial dose in severe stress (for example, sepsis, stroke), insulin resistance (for example, use of greater than >75 units per day), high-dose steroids, and so on. Adequate hydration, avoiding hypoglycemia, and measures to deal with underlying stress and infection are key to minimizing unstable glucose patterns.

MD note: Diabetic ketoacidosis is treated initially with 6 to 10 units/hr plus aggressive early hydration and cannot be managed alone with intravenous push insulin. Unlike simply poorly controlled diabetes, it is important to infuse glucose when blood glucose <200 mg/dL to avoid ketosis.

Monitoring and Titrating Insulin Infusion. Test blood glucose by bedside meter every hour until stable (range, 80–110 mg/dL) for two consecutive readings and then every 2 hrs.

Downward titration for rapid decline in blood glucose values.

| Current Blood Glucose Value | Amount Blood Glucose Decreased Within One Hour | Amount (%) to Decrease Insulin Infusion Rate |
|-----------------------------|--|--|
| ≥300 mg/dl | ≥200 mg/dl | 50% |
| <300 mg/dl | ≥100 mg/dl | 50% |
| <300 mg/dl | 50 to 99 mg/dl | 25% |
| 80–110 mg/dl | 25 to 49 mg/dl | 25% |

Adjust insulin infusion rate as follows:

| Blood Glucose Value mg/dl | Intervention |
|---------------------------|--|
| 65 or less | STOP infusion and follow Hypoglycemia Treatment Guidelines* |
| 66–79 | STOP infusion; restart at 50 % of prior rate when BG >110 mg/dl |
| 80–110 | No change in infusion rate |
| 111–150 | Increase rate by 0.5 units per hour after 2 BG results within this range |
| 151–200 | Increase rate by 1 unit per hour |
| 201–250 | Increase rate by 1.5 units per hour |
| Above 250 | Increase rate by 2 units per hour |

Call physician if blood glucose remains above 250 mg/dL for 3 consecutive hrs.

If tube feeding is discontinued for any reason, reduce insulin infusion rate by 50% and resume every 1 hr blood glucose checks.

Nursing Practice Guidelines. A second licensed healthcare provider will double-check to verify the medication, ordered dose, and dose programmed into the pump. This verification is done at:

Initiation of therapy: for accuracy of the medication label, concentration, ordered dose, and dose programmed into the pump;

All bag changes: for label accuracy compared with the physician's order, including concentration;

Change of direct nursing care provider: for accuracy of ordered dose on the protocol compared with the dose programmed into the pump, including concentration; and

Document the rate of insulin infusion and blood glucose results in a column on the CCFS. Document the drug, concentration, dose/rate verification with two

initials beside the column at the appropriate times.

Safety Recommendations. Use of the Panel Lock 1048753 feature on the IVAC pump is recommended during any high-risk infusion to prevent unauthorized changes of pump settings. See IVAC owner's manual for further assistance.

If a patient receiving an insulin infusion must travel off the unit for a procedure, a registered nurse must accompany the patient. Take the Insulin Infusion Travel Kit during transport after adding a glucose meter.

Avoid flushing the line that would inadvertently bolus the patient with insulin. If the intravenous access needs to be flushed, attach the flush syringe at the most proximal point possible.

Hypoglycemia Treatment Guidelines. Stop the infusion;

If patient is conscious and able to eat or drink, give 15 g of carbohydrate (CHO) in the form of:

Three to four glucose tablets; or
4 oz juice or regular soda or 1 cup skim milk.

Notify physician (MD). Recheck blood glucose in 15 mins and repeat treatment every 15 mins if needed until blood glucose is above 100 mg/dL.

If patient is unconscious or unable to eat or drink, give 25 mL (half amp) of dextrose 50% slow intravenous push or 1 mg glucagon intramuscularly STAT if no intravenous access. Notify MD. Recheck blood glucose in 15 mins and repeat treatment every 15 mins if needed until blood glucose is above 100 mg/dL.

Restart infusion when blood glucose >110 mg/dL at 50% of prior rate.

The MD should evaluate the cause of hypoglycemic episode.

Approved: Pharmacy & Therapeutics Committee (4/25/2003).

Revision Approved: Critical Care Committee (5/2/2005).