Intensive Insulin Therapy in Critical Care

A review of 12 protocols

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OBJECTIVE — To review performance characteristics of 12 insulin infusion protocols.

RESEARCH DESIGN AND METHODS — We systematically identify and compare 12 protocols and then apply the protocols to generate insulin recommendations in the management of a patient with hyperglycemia. The main focus involves a comparison of insulin doses and patterns of insulin administration.

RESULTS — There is great variability in protocols. Areas of variation include differences in initiation and titration of insulin, use of bolus dosing, requirements for calculation in adjustment of the insulin infusion, and method of insulin protocol adjustments. Insulin recommendations for a sample patient are calculated to highlight differences between protocols, including the patterns and ranges of insulin dose recommended (range 27–115 units [mean ± SD 66.7 ± 27.9]), amount recommended for glucose readings >200 mg/dl, and adjustments nearing target glucose.

CONCLUSIONS — The lack of consensus in the delivery of intravenous insulin infusions is reflected in the wide variability of practice noted in this survey. This mandates close attention to the choice of a protocol. One protocol may not suffice for all patients.

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Normalization of hyperglycemia in diabetes decreases morbidity and mortality (1,2). On the other hand, "stress hyperglycemia" of acute illness was considered an adaptive response to ensure an adequate fuel source for non-insulin-dependent tissues (e.g., red blood cells, the central nervous system) (3). The association of hyperglycemia with poor outcomes has challenged this view (4–6). Control of hyperglycemia in surgical intensive care unit (ICU) patients, those with acute coronary syndrome, and stroke improve outcomes (7–10). A mortality benefit to tight glycemic control in medical ICU (MICU) patients was suggested based on comparison with historical controls but was not substantiated in a prospective trial (11,12).

In 2004, the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) issued position statements for tight glycemic control of patients with critical illness in the surgical ICU (13,14). No specific recommendations were made for MICU patients, but the AACE stated that "it is reasonable [. . .] to assume that achievement of near-normal glycemia is beneficial and desirable in all ICU patients with elevated glucose," and their recommended blood glucose target during critical illness was <110 mg/dl (13). Others proposed a goal of 90–140 mg/dl (15). Both AACE and ADA have emphasized the importance of glucose control in their most recent consensus statement (16), which outlines crucial elements of a successful program, including adequate administrative support, multidisciplinary involvement, assessment of current practices, and standardized protocols. Crucial elements of the best protocols include adjustments for previous and current glucose levels, the rate of change in glucose, the insulin infusion rate, and the need for frequent glucose checks (16).

Protocols in the ICU decrease variability of practice and improve outcomes (17). Insulin infusion protocols decrease the time to and permit maintenance of a target blood glucose range and decrease hypoglycemia relative to sliding-scale insulin and physician-directed titration (18–20). Nevertheless, developing an insulin infusion protocol for the ICU has been challenging (19). A survey of published protocols is notable for their number and complexity (21). Intravenous insulin protocols have been designed for patients in both medical and surgical ICUs (20,22,23). Furnary and colleagues (24,25) describe a decade's worth of experience with incorporating changes to ensure patient safety and to prevent hypoglycemia and facilitate nursing utilization. Over time, they have decreased their target blood glucose from 150–200 mg/dl to 100–150 mg/dl to 80–120 mg/dl (26).

The most striking aspect of these protocols is the variability in insulin delivery and the complexity of instructions. This may result in great differences in insulin dosing and can be confusing for those trying to implement an insulin protocol. Our initial experience with an insulin protocol was notable for excess hypoglycemia and suboptimal dose titration. This led to the following review of published insulin protocols and comparison of insulin recommendations in a hyperglycemic MICU patient.

RESEARCH DESIGN AND METHODS

— A search for intravenous insulin protocols was performed using PubMed, the National Library of Medicine search engine, and the terms "insulin protocol" and "intravenous insu-

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Abbreviations: AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ICU, intensive care unit; MICU, medical ICU.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Comparison of insulin infusion protocols*

Author	Target glucose (mg/dl)	Bolus insulin		Changes in insulin infusion based on changes 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	15 h
Davidson	<180	N	N	N	N	Y	R	Multiplier	3/Y	7.5–10.5 h
Furnary	100–150	Y	Y	Y	Y	Y	R	U+%	2/Y	NR
Goldberg	100–139	Y	N	Y	Y	N	R+I	U+%	3/Y	9.0 h
Kanji	80–110	N	N	Y	Y	Y	R	U+%	2/Y	11.3 ± 7.9 h
Krinsley	<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	12–24 h
Watts	120–180	N	Y	N	N	N	R	U	1/N	8 h
Zimmerman	101–150	Y	Y	N	N	N	R+I	U+%	2/Y	2.1 h

See REFERENCES for complete citations. Protocols are all nursing driven with physician input written only for protocols by Bode and Van den Berghe. Bolus: Initial bolus = Y; Y* = variable dose based on physican input; Add = additional boluses based on glucose level. Changes in insulin infusion: Direction = reflect whether subsequent glucose levels are increasing or decreasing; Velocity = reflects changes based on the rate (amount) of decline in glucose; Resistance = adjustments based on patient's resistance to insulin. Basis of insulin change: R = rate changed based on glucose range; I = rate change based on insulin infusion rate; U = changes made in units of insulin; % = changes based on a percentage of the current insulin infusion rate; Multiplier = adjustment of insulin dose using a multiplier incorporated into a formula for calculation. Insulin adjustment: include number of steps and if calculations are needed. Time to goal: reported as median values, range, or mean ± SD. NR, not reported

lin." Protocols were limited to those designed for critically ill ICU patients. There is extensive experience with glucose-insulin-potassium infusions in myocardial infarction (27). These protocols were not included since they may not be applicable to other critically ill patients; free fatty acid reduction, not glucose control, was the intent for their use (28). Additional published protocols were identified by reviewing the publications' references.

With a single exception, the protocols represent efficacy studies, or protocols in use with historical controls. A systematic comparison of the performance of insulin protocols is not possible due to the lack of prospective, randomized trials. Therefore, this review focuses on the approach to intensive insulin therapy and differences between protocols.

A total of 12 different protocols were identified (7,11,15,19,25,29–36). Full-text review was conducted independently, and a consensus was achieved with respect to inclusion in the survey. For the purposes of discussion, the protocols are referred to by the first author and are listed in Table 1. Only the most recent published protocol was chosen in the case of similar protocols.

For example, the protocol published by Bode represents modifications of the protocols published by Markovitz and Trence (20,37). Similarly, the Ku protocol represents modifications from the Markovitz protocol (38). The Boord protocol is similar to protocols by Hirsch and Jacober (39,40). The Zimmerman protocol is similar to one by Brown (18). The Goldberg protocol provides more details of a protocol outlined by Metchick (23,41). The Furnary or Portland protocol is referenced by both its publication and online link (25,26). The published protocol was used for comparison. The Dilkhush protocol is similar to the Portland protocol (42). The Van den Berghe protocol was not originally published but subsequently available in supplementary materials (43). Protocols published by Herr, Levetan, and Laver (44–46) were not included because they were either lacking key details or too narrow in focus.

Some protocols have been incorporated into a computer program, accessed with a handheld computer or desktop. The Davidson protocol is one program and, while primarily a computerized program, is also available with options for bedside calculations. This protocol is also available in a drip-chart format that lists precalculated values (47). Other computerized guidelines have been reported but were not included because of their limited availability (48–50). One program by Thomas was based on the Van den Berghe protocol (49).

The protocols were reviewed with respect to target goals, autonomy, steps for initiation and titration of insulin, and methods of adjustment. The blood glucose records from a hyperglycemic patient treated with the Van den Berghe protocol at our institution were used to calculate insulin recommendations based on these protocols. The hourly blood glucose values during treatment were compared with the other 11 protocols using a blood glucose goal of 80–110 mg/dl. The major assumption was that the change in glucose would be the same for all of the protocols, allowing comparison of recommended insulin dosing. This methodology is similar that used by Davidson et al. (36). The reviewed patient data were from a comparative insulin study approved by our institutional review board, and the patient provided written informed consent for their participation.

RESULTS

The features of each protocol are presented in Table 1. There was variability in nearly every aspect of management. The following highlights the major differences between protocols.

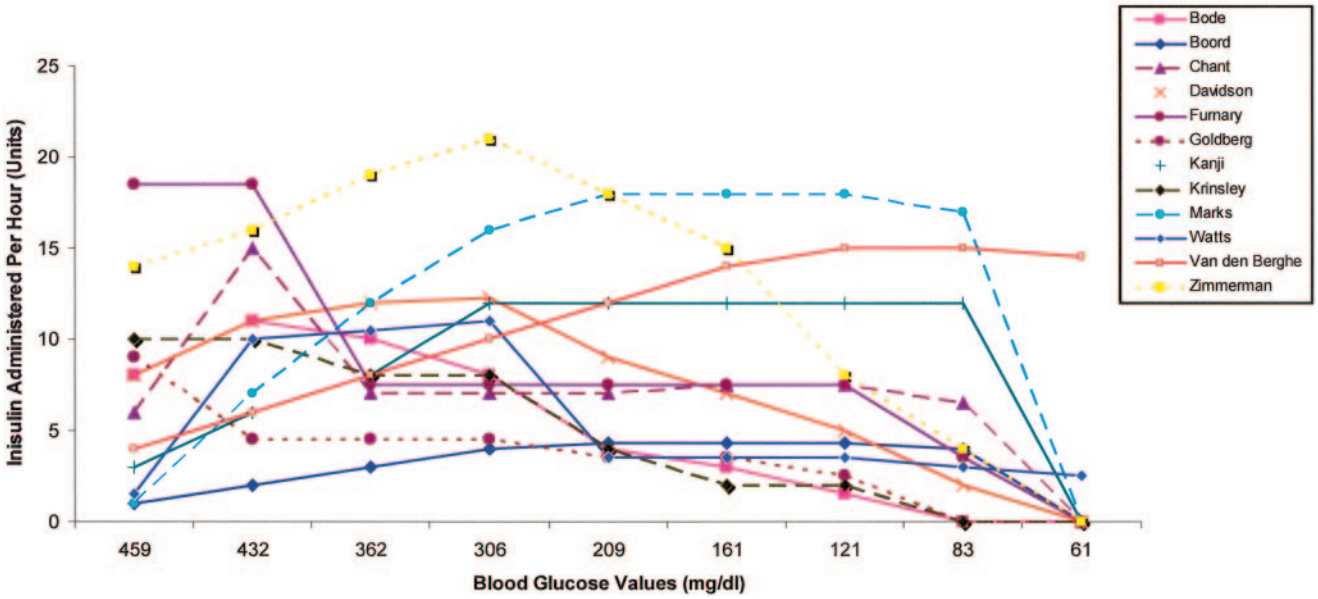

Figure 1—*Graphical summary of hourly insulin infusion rates using different insulin protocols to simulate treatment based on laboratory values from a hyperglycemic patient. See* REFERENCES *for citations.*

Staff implementation

The majority of protocols are nursing implemented with limited physician oversight. Only two specified initial physician input (Bode, Van den Berghe), and a physician assists the nursing staff with titration in the Van den Berghe protocol. All of the protocols, except the Furnary protocol, required administration of glucose while receiving intravenous insulin. Patients in the Van den Berghe protocol received 200–300 g of intravenous glucose per day or 20–30 kcal/kg of enteral/parenteral feedings.

Bolus insulin (initial and subsequent)

An initial insulin bolus was used in 4 of the 12 protocols. The bolus amount was based on the initial blood glucose value (Goldberg, Furnary, Zimmerman), whereas the Bode protocol left this to the discretion of the attending physician. Four protocols use subsequent bolus insulin to augment insulin titration (Chant, Furnary, Watts, Zimmerman).

Adjustments in infusion rate

Table 1 outlines the major differences. Four protocols require one step for adjustments in the insulin rate (Boord, Krinsley, Marks, Watts). Two-step protocols include those by Chant, Furnary, Kanji, Van den Berghe, and Zimmerman. The first three incorporate changes in the direction and amount of change in glucose to adjust the insulin rate. The Van den Berghe protocol does not require calculations to titrate insulin but does reduce the infusion for large (>50%) decreases in glucose. This protocol has been associated with frequent hypoglycemia, prompting one medical center to revise this protocol (19). This protocol allows and perhaps requires more physician oversight in adjusting the infusion, thereby precluding the need for more explicit step-by-step recommendations.

In 6 of the 12 protocols, the insulin infusion rate is adjusted based on the direction and/or the velocity (rate) of blood glucose decline. This represents additional steps and, in some, calculations before rate adjustment. Most changes are based on the glucose range, but two (Goldberg and Zimmerman) factor the insulin infusion rate in making adjustments. Changes in the infusion rate are made either in terms of absolute units or a percentage of the current insulin drip rate.

The Bode, Davidson, and Goldberg protocols require the greatest number of steps. The Bode protocol requires calculation of the rate of blood glucose change and duration in a given algorithm arm for each adjustment. The Davidson protocol uses a multiplier based on the blood glucose level. The Goldberg protocol factors both the direction of change in blood glucose and its velocity of change in adjustments. Eight of the 12 protocols require mathematical calculations of variable complexity.

Time to target glucose goals

The amount of time required to reach target glucose is reported for some of the protocols and outlined in Fig. 1. Direct comparison is tempered by noncomparable patients, but target levels are generally reached within 8–12 h and uniformly more rapidly than noted in previous experience with historical cohorts. Investigators also report lower mean morning serum glucose, lower proportion of hyperglycemic patients, slightly increased hypoglycemia, and greater nursing workload in patients treated with intravenous insulin infusions.

Insulin recommendations

The insulin recommendations for a hyperglycemic patient are presented in Fig. 1 and Table 2. The patient required a significant amount of insulin before control could be achieved. During the 9 h under evaluation, the patient actually received 98.5 units of insulin. Comparing the protocols, the amount of insulin recommended ranged from 26.9 to 115 units with a mean of 66.7 ± 27.9 units. There is considerable variability in the adjustment of the insulin infusion. With the blood glucose declining, 7 of the 12 protocols have the insulin rate either increasing or staying virtually the same (≤1 unit/h adjustment). Most protocols deliver the bulk (>75%) of the total insulin dose when the blood glucose levels is ≥200 mg/dl. Four protocols administer ≥45%

Table 2—*Comparison of insulin recommendations*

Author	Bolus (units)	Initial infusion rate (units/h)	Insulin infused with blood glucose >200 mg/dl (units)	Percentage of insulin infused with blood glucose >200 mg/dl	Highest hourly dose (units)	Total insulin dose (units)
Bode	0*	8	41	90%	11	45
Boord	0	1	14.3	53%	4.3	26.9
Chant	0	6	42	66%	15	63.5
Davidson	0	8	52.3	79%	12.3	66.3
Furnary	12	6.5	59.5	76%	18.5	78
Goldberg	4.5	4.5	26	81%	9	32
Kanji	3	3	41	53%	12	77
Krinsley	0	10	40	91%	10	44
Marks	0	1	54	50%	18	107
Van den Berghe	0	4	40	41%	15	98.5
Watts	0	1.5	36.5	74%	10.5	49
Zimmerman	10	4	88	77%	21	115

See REFERENCES for complete citations. *Protocol permitted a bolus amount at the discretion of the attending physician. For the purposes of this simulation, no bolus was incorporated into analysis.

of total insulin when the blood glucose is <200 mg/dl.

The Van den Berghe protocol calls for limited dose adjustment as the patient approaches hypoglycemia. As the blood glucose decreases from 83 to 61 mg/dl, the protocol called for a decrease from 15 to 14.5 units/h. Not surprisingly, the patient became hypoglycemic (<40 mg/dl). It should be noted that this represents actual experience with this protocol. While this protocol permits physician input in dosing adjustments, these are individualized adjustments and are not included in the written protocol.

CONCLUSIONS — Despite extensive experience with intravenous insulin infusions, there exists no uniformity in this arena. The lack of consensus is illustrated by the wide variability and different patterns of insulin administration noted in the above patient. This mandates close attention to the choice of a protocol. It is not clear that protocols developed and validated for postoperative patients are effective when applied to other critically ill patients. Critically ill medical patients may not respond in the same manner as postoperative patients because of fluctuations in circulating stress hormones, underlying diabetes, and other comorbidities. A single insulin protocol for an institution has merits, with uniformity as the main benefit, but may not be realistic.

Bode et al. (15) outline several features of an ideal insulin protocol, including the ability to adapt to an individual's response to insulin and the ability to balance stability and responsiveness. Braithwaite et al. (51) note the need for a standardized approach to the evaluation of these protocols, including patient-based measures of efficacy and measures of algorithm performance. We acknowledge and expand on points to consider when evaluating the efficacy and safety of any intravenous insulin protocol.

The first and foremost issue involves the approach to insulin delivery and adjustments. How is insulin initiated and titrated, and does the infusion anticipate and compensate for possible hypoglycemia? One strategy involves bolus insulin. Bolus insulin decreases the time to reach normoglycemia by administering a larger proportion of insulin "up front" as opposed to simply increasing the infusion rate.

Another strategy incorporates adjustments for variations in individual insulin resistance (reflected partly by adjustments based on the direction and velocity of glucose decline). This permits insulin-resistant patients to have doses titrated more aggressively than insulin-sensitive patients. The Bode protocol best illustrates this as the infusion rate is based on the degree of insulin resistance calculated with an insulin sensitivity factor. Other protocols account for the insulin resistance by multiplying the infusion rate by a constant (e.g., at 10 units/h, a 30% increase will lead to a 3-unit increase). Adjusting the insulin based on an absolute rather than a relative change does not account for insulin resistance and is presumably less effective in lowering the blood glucose. The multiplier used in the Davidson protocol adjusts for differences in insulin sensitivity.

It is impossible to compare the performance of a protocol without actually incorporating it into patient use. Compiling the differences between protocols with respect to recommendations and adjustment in the infusion rate provides some basis for comparison as illustrated in Table 1. However, ease of use, applicability to patients, insulin dose, and effectiveness of glucose control cannot be compared without its actual application in patients. A randomized trial comparing protocols in multiple patients is impractical. Applying multiple protocols to the same patient is likewise impractical. Therefore, the only comparison that can be made would be to compare the recommendations of these protocols with the response of a known patient.

The limitations to such a comparison are acknowledged since in real life, the glucose change would vary based on the insulin previously administered, changing subsequent glucose levels, which in turn influences infusion adjustments. On the other hand, this approach does illustrate the response of a protocol to observed glucose levels and provides insight into their performance. It incorporates the actual response of a patient so there is some basis for comparison between protocols. In this manner, it allows one to appreciate the different insulin infusion

patterns for the same situation. The differences seen are striking.

Noteworthy differences can be seen in the adjustments in dosing in the patient as the blood glucose approaches target. Five protocols (Bode, Davidson, Goldberg, Krinsley, and Zimmerman) decreased the insulin dose with declining blood glucose readings. These five protocols delivered the bulk (almost 80%) of insulin with the blood glucose >200 mg/dl. The other protocols either increased or maintained insulin infusions at a steady level as glucose declined, with four protocols giving close to 50% of the insulin with the blood glucose <200 mg/dl. This may increase the risk of hypoglycemia.

Other issues must be considered when evaluating an insulin protocol. The optimal degree of glycemic control and the impact of tight glycemic control in MICU patients remain undefined. Glucose control between 80 and 110 mg/dl is frequently cited because of the mortality benefit in postoperative surgical patients. Most of this data are from a single center, randomized trial (Van den Berghe). Furnary and colleagues (25) report near elimination of sternal wound infections and halving mortality with an intravenous insulin infusion. Krinsley (11) also noted an almost 30% reduction in mortality in a mixed medical-surgical ICU. While suggestive, their conclusions are tempered given their comparison to historical controls.

The benefit in MICU patients is not as clear. Van den Berghe (12) reported in a single center, prospective randomized trial, no significant reduction in mortality in an intent-to-treat analysis of 1,200 patients. It should be noted that their protocol was the same utilized for their postoperative patients. The mortality benefit with intensive insulin therapy occurred in those requiring ≥3 days of ICU care, and mortality was higher in those with a shorter stay. There was a decrease in morbidity defined as new renal insufficiency, duration of weaning from mechanical ventilation, and time to discharge from the ICU and hospital with intensive insulin therapy.

The risk of hypoglycemia must be factored into consideration of these protocols. The incidence of hypoglycemia (defined as a glucose ≤40 mg/dl) was in the 5% range in the Van den Berghe study of surgical patients but increased to 18.7% in the study with MICU patients and 25% in those with >3 days in the ICU (7,12). The odds ratio for hypoglycemia with intensive insulin therapy was 7.5 and would be higher with a threshold for hypoglycemia of 50 or even 60 mg/dl.

The upper threshold of optimal glucose control is undefined. A broader range of glucose and a higher threshold may be just as efficacious, easier to attain, and with a lower risk of hypoglycemia. Cross-sectional data from Krinsley and Finney suggest the upper threshold with respect to mortality lies somewhere between initial values of 145 and 180 mg/dl (5,6). In another analysis, increased mortality at a glucose of >150 mg/dl was noted but not apparent until >30 days had elapsed (52).

Intensive insulin therapy in MICU patients remains under study and has not received full endorsement (53). Two large, prospective, randomized trials are in progress, one in Europe and the other in Australia, New Zealand, and Canada (54,55). The GluControl trial will enroll 3,500 patients, and the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) will enroll 4,500 patients. Both studies will compare approximately the same ranges of glucose control (80–110 vs. 140–180 mg/dl).

The last issue involves protocol adjustments permitted by a written protocol. Physician oversight appears essential in some protocols. If nursing implemented protocols are utilized, there needs to be some allowance for "off-protocol" adjustments. A calculation more complex than simple subtraction or division increases the possibility of errors. It is unclear if increasing the precision (and therefore complexity) of insulin dosing translates into improved patient outcomes. While calculations may require no more than a minute, frequent adjustments add up. The patient described underwent 20 blood glucose determinations in the first 24 h of intravenous insulin therapy. Even 5 min per glucose determination translates to 100 min a day for insulin dosing. The experience and skill of nursing staff also contribute to a successful protocol. Concerns with calculations may be eased with nomograms or charts that require no calculation or automated computerized programs. Insulin adjustments are projected to require <5 min of nursing time, assuming a point-of-care glucose determination (23).

Recognition of the diversity of patients has led to the use of two separate insulin protocols (modified Furnary protocols) at our institution, one for the postoperative patient and the other for mainly MICU patients. The main differences involve a tighter range of glucose control with more rapid titration for hyperglycemia in postoperative patients.

Summary

In summary, the ideal insulin infusion protocol should achieve glycemic control in a reasonable timeframe, with minimal hypoglycemia, low operator error rate, and minimal nursing time required. The selection of a protocol requires careful investigation and must take the type of patient into account. The best incorporate bolus doses, adjust for the direction and rate of glucose decline, and permit "off-protocol" adjustments. Comparison of protocol insulin recommendations may be useful, but selection may not be possible short of an actual trial with the protocol. While "one protocol fits all" is a common practice, the diversity of patients call for a reexamination of this approach.

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