

INTRAVENOUS INSULIN INFUSION THERAPY: INDICATIONS, METHODS, AND TRANSITION TO SUBCUTANEOUS INSULIN THERAPY

Bruce W. Bode, MD, FACE, Susan S. Braithwaite, MD, FACE, FACP,
R. Dennis Steed, MD, and Paul C. Davidson, MD, FACE

ABSTRACT

Objective: To describe indications for intravenous (IV) insulin infusion therapy and glycemic thresholds, discuss methods and protocols, and promote use of and access to IV insulin infusion therapy for all appropriate patients in the hospital setting.

Results: Randomized, prospectively designed trials support the use of IV insulin infusion therapy for patients in the surgical intensive-care unit, including postoperative cardiac patients and patients having myocardial infarction. Among patients in the surgical intensive-care unit, reanalysis of the data suggested no threshold at which benefit occurred above the blood glucose level of 110 mg/dL. In another study, retrospective analysis of data among critically ill medical and surgical patients suggested a target blood glucose level of 145 mg/dL or less. In other populations, the threshold or ideal target blood glucose range has not been determined. Three protocols for IV insulin infusion are described that maintain blood glucose levels safely below the upper limit of their respective target ranges without substantial risk of hypoglycemia.

Conclusion: The threshold for initiation of IV insulin infusion is 110 mg/dL for critically ill surgical patients, 140 mg/dL for other medical or surgical patients, 180 mg/dL for patients in whom subcutaneous insulin regimens fail, and 100 mg/dL for pregnant women. The blood glucose target range is 80 to 110 mg/dL for selected critically ill surgical patients, 70 to 100 mg/dL for pregnant women, and 90 to 140 mg/dL for all other patients. Hospitals should develop procedures to make IV insulin infusion therapy available to all appropriate patients. (*Endocr Pract.* 2004;10[Suppl 2]:71-80)

Abbreviations:

BG = blood glucose; **ICU** = intensive-care unit; **IV** = intravenous; **SC** = subcutaneous; **TPN** = total parenteral nutrition

INDICATIONS

The medical literature supports the use of intravenous (IV) insulin infusion in preference to the subcutaneous (SC) route of insulin administration for several clinical indications, including diabetic ketoacidosis and nonketotic hyperosmolar state (1,2), critical care illness (3-5), myocardial infarction or cardiogenic shock (6-10), and the postoperative period after cardiac surgical procedures (11-15). Although the level of evidence is weaker with respect to outcome data, other indications for IV insulin infusion therapy include patients with type 1 diabetes who are being given nothing by mouth (16); general perioperative care, including organ transplantation (3,17-29); total parenteral nutrition (TPN) (30-33); hyperglycemia during high-dose corticosteroid therapy (34); stroke (35); use as a dose-finding strategy, anticipatory to initiation of SC insulin therapy in patients with type 1 or type 2 diabetes (36-39); labor and delivery; and other acute illnesses for which prompt glycemic control is judged important for recovery, such as prevention or treatment of infection (40-42).

For appropriately selected candidates, the recommended glycemic threshold for initiation of IV insulin infusion therapy is summarized in Table 1 (3,43).

Some patients can be managed safely with SC administration of insulin. During many medical illnesses such as acute gastroenteritis or gastroparesis with vomiting, or during prolonged "nothing by mouth" status, the use of IV insulin infusion is often necessary to control blood glucose (BG). For patients on general hospital wards, a decision to abandon SC insulin therapy depends on the response to current therapy and whether the patient is at the target BG level. Repeated doses of SC rapid-acting insulin analogue can be administered at 2-hour intervals to attempt to achieve BG control for appropriately selected but not critically ill patients. A reasonable guideline for conversion to IV insulin infusion therapy is failure to maintain the target

From Atlanta Diabetes Associates and Piedmont Hospital, Atlanta, Georgia.

Presented at the American College of Endocrinology Inpatient Diabetes and Metabolic Control Conference, Washington, DC, December 14 and 15, 2003.

© 2004 AACE.

Table 1
Thresholds for Initiation of
Intravenous Insulin Infusion Therapy*

Situation	Glucose threshold (mg/dL)
Perioperative care	>140
Surgical ICU care	>110-140†
Nonsurgical illness	>140-180‡
Pregnancy	>100

*ICU = intensive-care unit; IV = intravenous.

†The study by Van den Berghe et al (3) supports 110 mg/dL; the study by Finney et al (43) supports 145 mg/dL.

‡The patient who will start IV insulin infusion therapy because of failure of subcutaneous management might have a higher threshold for initiation of the infusion than the patient who requires IV insulin infusion because of medical conditions, such as myocardial infarction or type 1 diabetes with “nothing by mouth” status.

BG level with correction-dosed SC insulin therapy after 6 hours.

The threshold for initiation of an IV insulin infusion is defined by failure to maintain target BG values. Preoperative insulin infusion may be initiated for any surgical procedure in patients with type 1 or 2 diabetes as the preferred method to prevent glucose excursions from exceeding target range or for preoperative correction of hyperglycemia. For the patient with diabetes undergoing an elective surgical procedure who previously received basal insulin by injection, an appropriate approach is to perform frequent glucose monitoring preoperatively and intraoperatively and to begin an insulin infusion when the glucose level is 140 mg/dL or more. Because of concern about perfusion of SC sites, the reliability of the delivery of basal insulin by continuous SC insulin infusion is questionable. Therefore, pump therapy should be replaced with IV insulin infusion from the start in critical care patients. Some medical centers continue SC insulin pump therapy for minor surgical procedures.

During TPN, enteral nutrition, or corticosteroid therapy, any BG measurement above 140 mg/dL should trigger initiation of IV insulin therapy. For any patient in the surgical intensive-care unit (ICU) who does not have known diabetes, a BG level exceeding 140 mg/dL predicts persistent above-target values and the need for IV insulin therapy. For patients in the surgical ICU just returning from the operating room, an initial BG value of more than 140 mg/dL can be treated with an IV bolus of insulin or a single SC injection of rapid-acting insulin, calculated by

using the following formula: $(BG - 100)/30 =$ units of rapid-acting insulin. This correction dose should be repeated every 2 hours. If hyperglycemia (BG levels exceeding 140 mg/dL) persists at 6 hours, the patient should then be given IV insulin infusion therapy.

METHODS FOR IV INSULIN INFUSION

Numerous methods for IV insulin infusion therapy have been published (3-6,10,14,16,21,36,39,44-50). The ideal IV insulin infusion method should be effective with minimal risk of hypoglycemia, easily used in all hospital units including any outpatient unit, easily prescribed, easily implemented, and cost-effective. Few methods meet all these criteria. It is beyond the scope of this report to discuss all the major protocols published. Instead, basic components of the IV insulin infusion therapy will be discussed, and three sample algorithms are presented in Appendices 1, 2, and 3.

Insulin Concentration

IV insulin infusion is generally prepared by mixing regular insulin with 0.9% saline in a 1-to-1 ratio (250 U of regular insulin in 250 mL of 0.9% saline) or 0.5-to-1 ratio (125 U of regular insulin in 250 mL of 0.9% saline). The drip is then piggybacked into an IV fluid line, and the infusion rate should be at least 40 mL/h. The rate is controlled by an infusion pump that the nurse can adjust as directed by the algorithm. Of importance, the infusion pump must be able to deliver accurately 0.1 U/h increments in insulin infusion rate; if necessary, the concentration of the insulin used in the IV drip must be adjusted accordingly.

BG Monitoring

Monitoring of BG is done by using methods approved by hospital policies. Bedside monitoring, instead of central laboratory monitoring, should always be used to make hourly adjustments in the insulin drip, inasmuch as point-of-care results are favored over laboratory accuracy. The source of blood is usually a finger-stick or arterial line. The frequency of BG monitoring is directed by the specific algorithm. Most algorithms recommend a BG determination every hour until results are stable, at which point measurements should be done every 2 hours. Every-4-hour BG monitoring is not recommended.

Hospital Setting

In the hospital, IV insulin infusion therapy should be available for use anywhere, including the emergency department, outpatient holding areas, operating rooms, ICU, and general medical and surgical wards. Restriction of IV insulin infusion to the ICU prevents appropriate candidates from receiving the benefits of this therapy at critical times. The entire medical staff should be involved in developing pathways for implementing hospital-wide use of IV insulin infusion therapy.

Glucose Target Ranges for IV Insulin Infusion Therapy

The glucose target ranges for IV insulin therapy depend on the goals of treatment in specific situations. In the surgical setting, the study by Van den Berghe et al (3) suggested that those patients randomized for maintenance of the BG level at a value between 80 and 110 mg/dL had a better prognosis than did those randomized to a BG target of 180 to 200 mg/dL. A retrospective analysis of the data suggested there was no threshold at which benefit occurred above the upper limit of the normal fasting glycemic range, 110 mg/dL. In contrast, Finney et al (43), in a retrospective study of 523 surgical ICU patients, suggested a speculative upper limit of 145 mg/dL for the target BG level. In the nonsurgical setting, data in the areas of cardiac disease, infection control, and metabolic control support assignment of target BG levels to a range below 180 mg/dL, but little evidence supports the necessity of maintaining BG levels in the normal fasting range. In fact, in the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (6) and subsequent work with glucose-insulin-potassium therapy for cardiac disease, glycemic control was not the direct goal of IV insulin therapy; rather, an infusion of glucose, insulin, and potassium in a fixed ratio was used (8,9). Adjustments of the infusion were made if the BG concentration declined outside a target range of 126 to 200 mg/dL.

Because patients are asked to obtain near-normal BG levels at home, a similar goal in the hospital setting is reasonable. During labor and delivery, control of BG should be the same as during pregnancy. Of note, one of the principal barriers to widespread implementation of IV insulin infusion therapy is the fear that therapy targeted at a lower glycemic range might increase the risk of hypoglycemia, as it does during intensification of SC insulin therapy in the ambulatory setting. In fact, in comparison with SC insulin therapy, the frequent monitoring and brief duration of action of IV insulin therapy probably reduce the risk of hypoglycemia (51). Suggested BG target ranges during IV insulin infusion therapy are outlined in Table 2 (1,2,52,53).

Specific IV Insulin Infusion Algorithms

Numerous algorithms for IV insulin infusion are in clinical use; however, few have been subjected to analysis. Studied algorithms that work seem to have certain characteristics in common.

First, algorithms must be designed to reach the target BG range by adapting to the individual's response to insulin. Algorithms that rely on a fixed relationship between infusion rate and BG cannot seek and maintain target BG levels.

Second, algorithms must deal with the limited availability of glucose data in the clinical setting. There are practical limits to how often point-of-care BG can be monitored. For safety and the practical consideration of

Table 2
Suggested Glucose Target Ranges for Intravenous Insulin Infusion Therapy*

Patient population	Glucose (mg/dL)
Critically ill surgical patients	80-110
Other surgical and nonsurgical patients	90-140
Women during labor and delivery	70-100

*The American Diabetes Association clinical practice recommendations propose a target range during initial treatment of 150 to 200 mg/dL for patients with diabetic ketoacidosis and 250 to 300 mg/dL for patients with the hyperosmolar hyperglycemic syndrome to minimize the risk of cerebral edema, but there are no data to support this recommendation (1,2,52,53).

workload, algorithms should be able to vary the interval between glucose measurements on the basis of BG trending.

Finally, algorithms must balance stability and responsiveness. An aggressive algorithm may overshoot the BG target and result in oscillation between hyperglycemia and hypoglycemia. In contrast, an algorithm that is slow to reach a target BG level may subject a patient to unnecessarily prolonged periods of hyperglycemia or hypoglycemia and fail to respond to changing clinical situations.

Ultimately, the implementation of any algorithm is dependent on orders that can communicate effectively. Orders must be unambiguous and understandable. Unfortunately, many orders in clinical use require the nursing staff to remember or review the sequence of previous actions and then to perform detailed calculations. Three examples of orders of IV insulin infusion therapy are presented in the appendices of this report; the first is a protocol from Van den Berghe et al (3,5,54), and the other two (14,44) are used clinically by the authors of this report.

The algorithm of Van den Berghe et al (3,5,54), which was used in the Leuven postsurgical ICU study, is shown in Appendix 1. This algorithm adjusts the insulin infusion to obtain BG levels in the range of 80 to 110 mg/dL. Hypoglycemia, defined as a BG level of less than 40 mg/dL, occurred in 5.2% of patients. No patients had seizures or convulsions. With use of this algorithm, the nurses are required to make many decisions. The ambiguity and complexity of the algorithm and the imposed decision making limit its use to an ICU setting.

The algorithm of Braithwaite et al, shown in Appendix 2, was first published in *Endocrine Practice* by Markovitz et al (14), then revised by Trence, Kelly, and

Hirsch (10), and subsequently modified to achieve a target range BG of 100 to 150 mg/dL. It is currently used at the University of North Carolina–Chapel Hill. In this protocol, the columns are selected to maintain the BG level within the target range. The corrective insulin infusion rates were calculated by the rule of 1,500. This method has the feature of seeking a target. The initial order is to begin at column 2 and to switch columns on the basis of the patient's response. The BG is measured at hourly intervals; if results are stable, the intervals can be increased to 2 hours, with reversion to more frequent measurements in periods of instability. Multiple complicated decision points are avoided.

Postoperative heart patients were studied by comparing historical controls with patients treated under the IV insulin infusion protocol followed by SC insulin therapy managed by an endocrinologist. On postoperative day 1, when most patients received IV insulin infusion for at least part of the day, the average BG level exceeded the target value in 61% of historical control patients versus 21% of protocol-managed patients.

The algorithm of Davidson et al (44), widely used in numerous hospitals both as a manual drip and later as a computerized version (45,50), is outlined in Appendix 3. This algorithm was based on a prior study by White et al (36), who showed that IV insulin infusion in a pediatric clinical research center resulted in the equivalent of any BG level above 60 mg/dL times a sliding scale factor—which in the pediatric center was approximately 0.02. The formula was then adapted to vary this insulin sensitivity factor, known as the multiplier, to seek the appropriate glycemic target in all individual patients. The following formula was developed:

$$\text{Insulin (units per hour)} = \text{multiplier} \times (\text{BG} - 60)$$

With use of this algorithm manually, the initial multiplier is set at 0.02, and a BG value is determined every hour in conjunction with calculation of the units of IV insulin therapy per hour. The multiplier is adjusted every hour by 0.01 to obtain the target BG level—if the result is less than the target, decrease by 0.01; if within target range, no change is needed; if more than the target and the BG level has not decreased by 25%, increase by 0.01. The BG is always determined hourly until stable results are achieved; then it is measured every 2 hours.

In 1984, Steed and Davidson computerized this algorithm and developed the Glucommander, which automatically calculates the units per hour of insulin based on the BG level and the insulin sensitivity of the specific patient (44,45). The Glucommander automatically adjusts the multiplier by learning the patient's insulin sensitivity. In addition, the Glucommander seeks the target BG range specified by the ordering physician. It sounds an alarm for determination of BG values at variable intervals. The timing of glucose measurement is usually every hour, but it

can be every 20 minutes in rapidly changing BG values and every 2 hours once the BG is stable in the target range.

This computerized system has been widely accepted in all areas of our 600-bed tertiary referral medical center as well as more than 50 other US hospitals. More than 120,000 hours of experience with at least 5,800 cases with the Glucommander have been analyzed. The median BG value at initiation was 309 mg/dL (range, 66 to 1,192), the median time to achieve a BG level of less than 180 mg/dL was 2.6 hours (range, 0 to 12.2), the median duration of use was 21.5 hours (range, 4.5 to 117), and the total percentage of BG values less than 60 mg/dL was 0.4%. Only 2.6% of 5,772 Glucommander runs have included a BG level less than 40 mg/dL—in comparison with 5.2% in the series reported by Van den Berghe et al (3,5,54). In all cases, the Glucommander's recommendations have been appropriate and consistent with those of experienced clinicians. Any deviations have resulted from such factors as interruptions in IV fluids or tube feedings, improper entry of initial measurements, disconnected insulin infusion pumps, or provision of trays of food when patients should not have received them. In general, the Glucommander has made appropriate and reasonable recoveries from these operating errors.

Regardless of the details of the protocol selected by an institution, a multidisciplinary effort will help promote the spread of use of IV insulin infusion therapy to appropriate wards and patients (47).

Correction of Hypoglycemia

A policy for correction of hypoglycemia should be the standard of care at all hospitals. The preferred treatment of hypoglycemia is IV administration of dextrose when IV access is available. The amount of glucose to give is dependent on the BG level at that time and the patient's weight. In a normal-weight patient, 25 g of glucose will raise the BG level by approximately 125 mg/dL. The following formula can be used for correction of hypoglycemia:

$$(100 - \text{current BG}) \times 0.4 = \text{amount (mL) of 50\% dextrose IV}$$

Such precise treatment with 50% dextrose IV is effective without overcorrection or undercorrection of BG to a target value of 100 mg/dL (55).

Supplemental Feedings and IV Fluids

Of importance, glucose intake (in the form of either IV fluids or enteral feedings) should be kept constant during IV insulin infusion therapy. Most algorithms can accommodate a slow increase or decrease in glucose intake, but none can manage a substantial change in glucose intake without destabilization of the BG level. If oral feeding is attempted, administer an additional SC bolus of rapid-acting insulin (1 U for every 10 g of carbohydrate consumed) in addition to continuing the IV insulin infu-

sion. If glucose intake is abruptly stopped (for example, removal of a feeding tube or discontinuation of TPN), immediately decrease, reset, or discontinue the insulin drip until glucose intake is resumed.

CONVERSION FROM IV TO SC INSULIN THERAPY

Conversion from IV insulin infusion to SC insulin therapy should be postponed until volume resuscitation or pressor support can be discontinued and the patient is ready to resume eating. Scheduled SC insulin therapy should meet basal and nutritional insulin requirements and should include correction doses for hyperglycemia. SC administration of insulin should be initiated at least 2 hours before discontinuation of the IV insulin infusion in most patients. It may be wise to implement basal insulin in the form of a long-acting peakless analogue (for example, glargine) in conjunction with the IV insulin infusion therapy to expedite the transition to SC therapy. A minority of patients may not require transition to SC insulin therapy, although ongoing glucose monitoring in the hospital should be done and correction doses should be administered as needed. These are patients with type 2 diabetes or patients with no prior history of diabetes whose BG levels are well controlled with less than 0.5 U of IV insulin therapy per hour.

An estimation of the 24-hour IV insulin requirement can be extrapolated from the average amount of insulin infused during the previous 6 to 8 hours. This process should be done after the patient is not receiving pressor agents and the BG level is stable in the target range.

During sharply curtailed caloric intake, the requirements for IV insulin infusion closely approximate the daily basal insulin requirement. After heart operations, patients often receive little dextrose and eat poorly. In the morning, the current basal insulin requirements can usually be estimated from the preceding 6 to 8 hours overnight (38). Approximately 80% of the projected 24-hour basal insulin requirement is administered SC as the first daily injection of peakless long-acting insulin glargine; the mean overnight insulin drip rate in units per hour can be multiplied by 20 hours to calculate the initial loading dose of glargine. This dose should be continued each evening and adjusted; most likely, it should be reduced on the basis of the patient's response. After the first dosing of glargine, it is prudent to order a glucose test for the mid-sleep period and to treat with IV administration of glucose if the result is less than 80 mg/dL. As appetite improves, the prandial insulin dose is increased until approximately equal amounts of basal and bolus insulin are administered. It must be emphasized that no guidelines for such a transition after cardiac surgical procedures have been validated in published trials.

During completely normal oral intake or during administration of IV dextrose or enteral feedings, the 24-hour insulin requirement during IV infusion of insulin

estimates the combined basal and nutritional requirements. The components of SC insulin regimens that replace the IV insulin infusion should be appropriately apportioned to cover basal and nutritional requirements (49,50,56,57). Again, the total daily dose of scheduled SC insulin therapy is assigned conservatively for most patients to be 80% of the amount projected for 24 hours after overnight observation with use of minimal IV administered glucose (that is, 125 mL/h of 5% dextrose).

Correction doses for hyperglycemia are given preferably as a rapid-acting insulin analogue. The correction dose is administered before meals, at bedtime, and at 3 AM in patients who are eating or every 4 to 6 hours in patients who are receiving continuous feeding or nothing by mouth. To determine the correction dose, one must estimate how much the BG level is lowered by 1 U of rapid-acting insulin. This factor is called the correction factor or insulin sensitivity factor and is estimated by dividing the total daily dose into 1,700 (49,50,56). On average, 1 U of rapid-acting insulin lowers the BG level by 30 to 50 mg/dL. The formula for the correction dose is the actual BG level (determined by finger-stick) minus the target BG (usually 100 mg/dL) divided by the correction factor. An example of the formula used in the transition from IV to SC insulin therapy is shown in Table 3.

As stated earlier, the IV insulin infusion should not be discontinued until at least 2 hours after the first doses of rapid- or short-acting insulin (or longer with long-acting insulin) have been given. The requirement for continuity of effect is especially important for insulin-deficient patients, who are at risk for ketoacidosis. Patients must have no gap in coverage for glycemic control before the effect of the long-acting insulin is available. If the patient is being dismissed from the hospital with this new basal-bolus insulin regimen, it is imperative that the patient or caregivers be instructed in a plan for BG monitoring as well as administration and adjustment of basal, bolus, and correction doses. Arrangements must be made for timely follow-up with the health-care provider and diabetes team. Home health-care assistance may be required.

AREAS NEEDING FURTHER INVESTIGATION

Many questions remain unanswered. The following is a list of some questions that should be addressed in future outcome trials:

1. Are there more appropriate threshold BG target ranges for using IV insulin infusion among critically ill surgical patients, including postoperative heart patients and patients having acute myocardial infarction?
2. What are the appropriate BG target ranges for other surgical and medical conditions treated in the hospital? Are there indications for insulin therapy among normoglycemic patients?

Table 3
Example of Transition From
Intravenous to Subcutaneous Insulin Therapy*

<p>Patient has received an average of 2 U/h IV during previous 6 h. Recommended doses are as follows:</p> <p>SC TDD is 80% of 24-h insulin requirement: 80% of (2 U/h × 24) = 38 U</p> <p>Basal dose is 50% of SC TDD: 50% of 38 U = 19 U of long-acting analogue</p> <p>Bolus total dose is 50% of SC TDD: 50% of 38 U = 19 U of total prandial rapid-acting analogue or ~6 U with each meal</p> <p>Correction dose is actual BG minus target BG divided by the CF, and CF is equal to 1,700 divided by TDD: CF = 1,700 ÷ 38 = ~40 mg/dL Correction dose = (BG - 100) ÷ 40</p>
<p>*BG = blood glucose; CF = correction factor; IV = intravenously; SC = subcutaneous; TDD = total daily dose.</p>

- In comparison with SC administration of insulin, for which conditions does IV insulin infusion therapy show net benefit in reducing hyperglycemia and providing safety from hypoglycemia?
- Is IV insulin infusion for each of these conditions practical and cost-effective? What strategies will help to promote the use of IV insulin infusion throughout the hospital for all appropriate patients?
- What is the safest and most efficacious IV insulin infusion algorithm that can be used hospital-wide? Should the algorithm be computerized to minimize errors, enhance acceptability, and encourage adoption by all providers?
- In transitions from IV to SC therapy, what conversion rules can be shown to be efficacious and safe?

CONCLUSION

Clinical evidence continues to accumulate, showing that normalization of BG levels with IV insulin therapy in the hospital setting improves outcomes. Until next-generation closed-loop systems are available for management of patients, it is important to develop and use protocols that can safely and effectively help achieve this goal. The indications for IV insulin infusion therapy, the glycemic thresholds for initiation of IV insulin therapy, the glycemic targets of IV insulin therapy, the desirable features of algorithms, and some practical experience translating algorithms to clinical practice were presented. The transition from IV to SC insulin therapy was also dis-

cussed. Many unanswered questions remain, and further investigation in this area is needed.

REFERENCES

- Kitabchi AE, Umpierrez GE, Murphy MB, et al.** Management of hyperglycemic crises in patients with diabetes. *Diabetes Care.* 2001;24:131-153.
- Kitabchi AE, Umpierrez GE, Murphy MB, et al (American Diabetes Association).** Hyperglycemic crises in patients with diabetes mellitus. *Diabetes Care.* 2003;26(Suppl 1):S109-S117.
- Van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;19:1359-1367.
- Brown G, Dodek P.** Intravenous insulin nomogram improves blood glucose control in the critically ill. *Crit Care Med.* 2001;29:1714-1719.
- Van den Berghe G, Wouters PJ, Bouillon R, et al.** Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med.* 2003;31:359-366.
- Malmberg K, Rydén L, Efendic S, et al.** Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* 1995;26:57-65.
- Malmberg K (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction [DIGAMI] Study Group).** Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ.* 1997;314:1512-1515.
- Lazar HL, Philippides G, Fitzgerald C, Lancaster D, Shemin RJ, Apstein C.** Glucose-insulin-potassium solutions enhance recovery after urgent coronary artery bypass

- grafting [with discussion]. *J Thorac Cardiovasc Surg.* 1997;113:354-362.
9. **Lazar HL, Chipkin S, Philippides G, Bao Y, Apstein C.** Glucose-insulin-potassium solutions improve outcomes in diabetics who have coronary artery operations. *Ann Thorac Surg.* 2000;70:145-150.
 10. **Trence DL, Kelly JL, Hirsch IB.** The rationale and management of hyperglycemia for in-patients with cardiovascular disease: time for change. *J Clin Endocrinol Metab.* 2003;88:2430-2437.
 11. **Gill GV, Sherif IH, Alberti KG.** Management of diabetes during open heart surgery. *Br J Surg.* 1981;68:171-172.
 12. **Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A.** Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg.* 1997;63:356-361.
 13. **Furnary AP, Zerr KJ, Grunkemeier GL, Starr A.** Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures [with discussion]. *Ann Thorac Surg.* 1999;67:352-362.
 14. **Markovitz LJ, Wiechmann RJ, Harris N, et al.** Description and evaluation of a glycemic management protocol for diabetic patients undergoing heart surgery. *Endocr Pract.* 2002;8:10-18.
 15. **Furnary AP, Gao G, Grunkemeier GL, et al.** Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;125:1007-1021.
 16. **Hirsch IB, Paauw DS, Brunzell J.** Inpatient management of adults with diabetes. *Diabetes Care.* 1995;18:870-878.
 17. **Walts LF, Miller J, Davidson MB, Brown J.** Perioperative management of diabetes mellitus. *Anesthesiology.* 1981;55:104-109.
 18. **Alberti KG, Gill GV, Elliott MJ.** Insulin delivery during surgery in the diabetic patient. *Diabetes Care.* 1982;5(Suppl 1):65-77.
 19. **Thomas DJ, Platt HS, Alberti KG.** Insulin-dependent diabetes during the peri-operative period: an assessment of continuous glucose-insulin-potassium infusion, and traditional treatment. *Anesthesia.* 1984;39:629-637.
 20. **Husband DJ, Thai AC, Alberti KG.** Management of diabetes during surgery with glucose-insulin-potassium infusion. *Diabet Med.* 1986;3:69-74.
 21. **Watts NB, Gebhart SS, Clark RV, Phillips LS.** Postoperative management of diabetes mellitus: steady-state glucose control with bedside algorithm for insulin adjustment. *Diabetes Care.* 1987;10:722-728.
 22. **Pezzarossa A, Taddei F, Cimicchi MC, et al.** Perioperative management of diabetic subjects: subcutaneous versus intravenous insulin administration during glucose-potassium infusion. *Diabetes Care.* 1988;11:52-58.
 23. **Hirsch IB, McGill JB.** Role of insulin in management of surgical patients with diabetes mellitus. *Diabetes Care.* 1990;13:980-991.
 24. **Alberti KG.** Diabetes and surgery. *Anesthesiology.* 1991;74:209-211.
 25. **Gavin LA.** Perioperative management of the diabetic patient. *Endocrinol Metab Clin North Am.* 1992;21:457-475.
 26. **Schiff RL, Emanuele MA.** The surgical patient with diabetes mellitus: guidelines for management. *J Gen Intern Med.* 1995;10:154-161.
 27. **Gill GV, Alberti KGMM.** The care of the diabetic patient during surgery. In: Alberti KGMM, Zimmet P, DeFronzo RA, eds. *International Textbook of Diabetes Mellitus.* Chichester: Wiley, 1997: 1243-1254.
 28. **Avilés-Santa L, Raskin P.** Surgery and anesthesia. In: Lebovitz HE, ed. *Therapy for Diabetes Mellitus and Related Disorders.* 3rd ed. Alexandria, VA: American Diabetes Association, 1998: 224-233.
 29. **Skyler J.** Surgery. In: Kelley DB, ed. *Medical Management of Type 1 Diabetes.* Alexandria, VA: American Diabetes Association, 1998: 159-163.
 30. **Woolfson AM.** Control of blood glucose during nutritional support in ill patients. *Intensive Care Med.* 1980;7:11-14.
 31. **Woolfson AM.** An improved method for blood glucose control during nutritional support. *JPEN J Parenter Enteral Nutr.* 1981;5:436-440.
 32. **Knapke CM, Owens JP, Mirtallo JM.** Management of glucose abnormalities in patients receiving total parenteral nutrition. *Clin Pharm.* 1989;8:136-144.
 33. **Park RH, Hansell DT, Davidson LE, Henderson G, Legge V, Gray GR.** Management of diabetic patients requiring nutritional support. *Nutrition.* 1992;8:316-320.
 34. **Braithwaite S.** Detection and management of diabetes mellitus during glucocorticoid therapy of nonendocrine disease. In: Meikle AW, ed. *Endocrine Replacement Therapy in Clinical Practice.* Totowa, NJ: Humana Press, Inc, 2003: 251-272.
 35. **Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS.** Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). *Stroke.* 1999;30:793-799.
 36. **White NH, Skor D, Santiago JV.** Practical closed-loop insulin delivery: a system for the maintenance of overnight euglycemia and the calculation of basal insulin requirements in insulin-dependent diabetics. *Ann Intern Med.* 1982;97:210-213.
 37. **Mokan M, Gerich JE.** A simple insulin infusion algorithm for establishing and maintaining overnight near-normoglycemia in type I and type II diabetes. *J Clin Endocrinol Metab.* 1992;74:943-945.
 38. **Mao CS, Riegelhuth ME, Van Gundy D, Cortez C, Melendez S, Ipp E.** An overnight insulin infusion algorithm provides morning normoglycemia and can be used to predict insulin requirements in noninsulin-dependent diabetes mellitus [erratum in *J Clin Endocrinol Metab.* 1998;83:876]. *J Clin Endocrinol Metab.* 1997;82:2466-2470.
 39. **Hawkins JB Jr, Morales CM, Shipp JC.** Insulin requirement in 242 patients with type II diabetes mellitus. *Endocr Pract.* 1995;1:385-389.
 40. **Golden SH, Peart-Vigilance C, Kao WH, Brancati FL.** Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care.* 1999;22:1408-1414.
 41. **Pomposelli JJ, Baxter JK III, Babineau TJ, et al.** Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr.* 1998;22:77-81.
 42. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab.* 2002;87:978-982.
 43. **Finney SJ, Zekveld C, Elia A, Evans TW.** Glucose control and mortality in critically ill patients. *JAMA.* 2003;290:2041-2047.
 44. **Davidson PC, Steed RD, Bode BW, Sivitz WI.** Computer-controlled intravenous insulin infusion using intermittent bedside glucose monitoring: one year's experience [abstract]. *Diabetes.* 1986;35(Suppl 1):126.

45. **Bode BW, Davidson GG, Mather SR, et al.** Evaluation of the glucose management system (GMS) for administering IV insulin therapy to hospitalized patients with diabetes [abstract]. *Diabetes.* 1999;48:A0519.
46. **Levetan CS, Magee MF.** Hospital management of diabetes. *Endocrinol Metab Clin North Am.* 2000;29:745-770.
47. **Quevedo SF, Sullivan E, Kington R, Rogers W.** Improving diabetes care in the hospital using guideline-directed orders. *Diabetes Spectrum.* 2001;14:226-233.
48. **Bode BW, Tamborlane WV, Davidson PC.** Insulin pump therapy in the 21st century: strategies for successful use in adults, adolescents, and children with diabetes. *Postgrad Med.* 2002;111:69-77.
49. **Bode BW, Tamborlane W, Davidson PC.** Intensive insulin therapy and insulin pumps. *Postgrad Med.* 2002;112:17-21.
50. **Bode BW, ed.** *Medical Management of Type 1 Diabetes.* 4th ed. Alexandria, VA: American Diabetes Association, 2003.
51. **Montori VM, Bistrian BR, McMahan MM.** Hyperglycemia in acutely ill patients. *JAMA.* 2002;288:2167-2169.
52. **Glaser N, Barnett P, McCaslin I, et al (Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics).** Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med.* 2001;344:264-269.
53. **Dunger DB, Edge JA.** Predicting cerebral edema during diabetic ketoacidosis. *N Engl J Med.* 2001;344:302-303.
54. **Van den Berghe G.** Insulin therapy in critical illness. *Int Diabetes Monitor.* 2002;14:1-6.
55. **Richardson P, Steed RD, Davidson PC.** Immediate correction of hypoglycemia without rebound using simple variable dosing of IV glucose [abstract]. *Diabetes.* 1999;48(Suppl 1):A363.
56. **Davidson PC, Hebblewhite HR, Bode BW, et al.** Statistically based CSII parameters: correction factor (CF) (1700 rule), carbohydrate-insulin ratio (CIR) (2.8 rule), and basal-to-total ratio [abstract]. *Diabetes Technol Ther.* 2003;5:237.
57. **Pitts DM, Kilo KA, Pontious SL.** Nutritional support for the patient with diabetes. *Crit Care Nurs Clin North Am.* 1993;5:47-56.

APPENDIX 1

Algorithm for Intravenous Insulin Infusion: Protocol of Van den Berghe et al (3,5,54)*

Test	BG result	Action
Measure glucose on entry to ICU	>220 mg/dL	Start insulin, 2-4 U/h
	110-220 mg/dL	Start insulin, 1-2 U/h
	<110 mg/dL	Do not start insulin; continue BG monitoring every 4 h
Measure glucose every 1-2 h until within normal range	>140 mg/dL	Increase insulin dose by 1-2 U/h
	110-140 mg/dL	Increase insulin dose by 0.5-1 U/h
	Approaching normal range	Adjust insulin dose by 0.1-0.5 U/h
Measure glucose every 4 h	Approaching normal range	Adjust insulin dose by 0.1-0.5 U/h
	Normal	Insulin dose unchanged
	Declining steeply	Reduce insulin dose by half; check BG more frequently
	60-80 mg/dL	Reduce insulin dose; check BG within 1 h
	40-60 mg/dL	Stop insulin infusion, ensure adequate baseline glucose intake, and check BG within 1 h
	<40 mg/dL	Stop insulin infusion, ensure adequate baseline glucose intake, administer glucose per 10-g IV boluses, and check BG within 1 h

*BG = blood glucose; ICU = intensive-care unit; IV = intravenous.

APPENDIX 2

Algorithm for Intravenous Insulin Infusion: Protocol of Braithwaite et al (14)*†

Column 1		Column 2		Column 3		Column 4		Column 5		Column 6	
BG	U/h	BG	U/h	BG	U/h	BG	U/h	BG	U/h	BG	U/h
<70	Off	<70	Off	<70	Off	<70	Off	<70	Off	<70	Off
70-79	Off	70-79	Off	70-79	Off	70-79	Off	70-79	0.5	70-79	1
80-89	Off	80-89	Off	80-89	Off	80-89	0.5	80-89	1	80-89	1.5
90-99	Off	90-99	Off	90-99	0.5	90-99	1	90-99	1.5	90-99	2
100-109	Off	100-109	0.5	100-109	1	100-109	1.5	100-109	2	100-109	3
110-129	0.5	110-129	1	110-129	1.5	110-129	2	110-129	3	110-129	4
130-149	1	130-149	1.5	130-149	2	130-149	3	130-149	4	130-149	6
150-179	1.5	150-169	2	150-179	3	150-169	4	150-179	6	150-169	8
		170-189	2.5			170-189	5			170-189	10
180-209	2	190-209	3	180-209	4	190-209	6	180-209	8	190-209	12
210-269	3	210-254	4	210-239	5	210-229	7	210-239	10	210-229	14
				240-269	6	230-269	8	240-269	12	230-249	16
270-329	4	255-299	5	270-299	7	270-309	10	270-299	14	250-269	18
		300-345	6	300-329	8	310-349	12	300-329	16	270-309	20
330-389	5			330-359	9			330-359	18	310-349	24
		346-389	7	360-389	10	350-389	14	360-389	20	350-389	28
≥390	6	≥390	8	≥390	11	≥390	16	≥390	22	≥390	32

*BG = blood glucose (mg/dL). Boldface entries denote target range.

†Note: Target BG range is 100 to 150 mg/dL. Each column represents a different insulin requirement for maintenance of target BG range. Each column shows BG and corresponding intravenous insulin infusion rate. Testing is done hourly until the patient meets criteria for stability, at which time testing is done every 2 h. The default instruction to nursing staff is to begin with column 2, with use of a priming bolus of insulin in amount dependent on glucose concentration. The staff is instructed under protocol to switch to the next higher column under the following circumstances:

- BG ≥200 mg/dL for 1 h and decreasing <30 mg/dL during past 1 h
- BG ≥150 mg/dL for 2 h and decreasing <60 mg/dL during past 2 h

The staff tests BG every 1 h if drip is turned off by protocol. After drip interruption for low BG, the staff resumes the insulin infusion when BG >109 mg/dL. The staff switches to the next lower column in either of the following circumstances:

- The infusion was interrupted for low BG but now is resuming *or*
- The patient has been on column 4, 5, or 6 for past 8 h, with BG within target range.

APPENDIX 3

Algorithm for Intravenous Insulin Infusion: Protocol of Bode et al (44,45,50) for Both Computer-Calculated and Registered Nurse-Calculated Intravenous Insulin Orders

1. Initiate blood glucose (BG) flow sheet.
2. Obtain intravenous (IV) insulin drip: 250 mL of normal (isotonic) saline (NS) with 125 U of regular insulin (0.5 U/mL). Piggyback insulin drip into IV fluids using IV controller. Do not filter insulin line.
3. Obtain initial BG level per hospital BG meter.
4. Indicate low target BG: 80 100 or _____mg/dL.
Indicate high target BG: 100 110 120 140 or _____mg/dL.
5. Diet: () NPO () Noncaloric clear liquids
Do not feed calorie-containing foods unless additional mealtime insulin is ordered.
6. Treatment for hypoglycemia: If BG <80 mg/dL, administer 50% dextrose IV according to the following formula:
(100 - BG) × 0.4 = mL of 50% dextrose by IV push.
7. Call physician if BG <60 mg/dL × 2; or >200 mg/dL × 4 after 4 hours of IV insulin infusion.
8. Call physician if patient requires >25 U (or >_____U) of insulin per hour.

Choose Order Set for: Glucommander (Computer Calculated) or Insulin Drip (Registered Nurse Calculated)

Glucommander (Computer Calculated)

- Obtain initial BG level, and *each time* the Glucommander beeps, enter the value into the Glucommander. The Glucommander will automatically calculate the units of insulin per hour and the units of insulin drip to adjust on the IV controller.
 - IV fluids (place on IV controller):
NS + _____mEq/L KCl at _____mL/h.
When BG <250 mg/dL, switch IV fluids to 5% dextrose + NS + _____mEq/L KCl at _____mL/h.
 - Multiplier: 0.02 or _____.
 - Maximum minutes between BG readings: 120 min or _____.
- Note:* Glucommander will beep for new BG more frequently until BG is stabilized. Obtain and enter BG value EVEN if insulin drip is at 0 U/h. The drip will be restarted if the BG level has increased.

Or

Insulin Drip Orders (Registered Nurse Calculated)

Starting drip rate:

Use the following formula: $(BG - 60) \times 0.02 = \text{units of insulin/h}$.

Formula description: BG is current blood glucose level, and 0.02 is the multiplier.

- Check BG level every hour per hospital BG meter and adjust insulin drip.
 - If BG level is in target range for 4 hours in a row, may check BG every 2 hours.
 - Adjust to current multiplier in drip from previous multiplier according to the following directions:
 1. When BG level is greater than HIGH target, increase multiplier by 0.01.
 2. When BG level is less than LOW target, decrease multiplier by 0.01.
 - When BG level is within target range, do not change multiplier, and adjust drip rate according to formula.
 - If treatment for hypoglycemia is needed (BG <80 mg/dL), decrease the multiplier by 0.01 and continue the insulin drip.
- Do not stop IV insulin drip if insulin rate is >0.5 U/h until subcutaneous insulin therapy is initiated. (BG values should be within target range for >4 hours before IV insulin infusion is discontinued.)