CLINICAL PRACTICE

Management of Hyperglycemia in the Hospital Setting

Silvio E. Inzucchi, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 53-year-old woman with asthma and multilobar pneumonia is admitted with respiratory failure. She is intubated and treated with antibiotics, albuterol, and methylprednisolone. A random blood glucose measurement obtained on admission shows a level of 183 mg per deciliter (10.2 mmol per liter). After 3 hours in the intensive care unit, she has a capillary glucose level of 264 mg per deciliter (14.7 mmol per liter). She has no history of diabetes. Should her hyperglycemia be treated, and if so, how?

THE CLINICAL PROBLEM

Until recently, hyperglycemia in hospitalized patients was considered to be little more than a paraphenomenon of illness. However, evidence that in certain circumstances aggressive therapy may improve clinical outcomes has brought increased attention to glucose management in the inpatient setting.[1-3]

The relationship between hyperglycemia and acute illness is a complex one.[1,3,4] Hyperglycemia is frequently encountered during hospitalization owing to increases in patients' circulating concentrations of stress hormones. In experimental models, severe hyperglycemia (generally characterized as a glucose level greater than about 250 mg per deciliter [13.9 mmol per liter]) has been shown to have deleterious effects on the vascular, hemodynamic, and immune systems (Fig. 1).[1,3,4] Several retrospective studies have shown that hyperglycemia is associated with poor outcomes in hospitalized patients. Postoperative glucose levels are a significant predictor of infection rates after cardiac surgery.[5,6] In a study of patients with diabetes and acute myocardial infarction, elevated levels of blood glucose at the time of admission predicted both in-hospital and 1-year mortality.[7] Similar findings have been reported for patients in medical intensive care units (ICUs),[8] general postsurgical patients,[9] and patients with other acute cardiovascular events, including stroke[10-12]; associations between glycemia and the risk of death remain significant even after adjusting for the severity of illness.[12]

These observations are not confined to patients with diabetes.[10-12] In one study, in-hospital mortality rates appeared to be even higher for patients with newly diagnosed hyperglycemia than for those with overt diabetes.[13] Such data, although provocative, cannot prove cause and effect; the question of whether glucose is a modifiable mediator of adverse outcomes or simply an innocent marker of critical illness remains unanswered. If glucose is in fact a mediator, aggressive therapy may be indicated. Clearly, intensive insulin administration and the need to monitor the patient come at a cost of time and money. Such therapy may also predispose patients to hypoglycemia, with attendant risks of transient or, in rare cases, permanent complications. What is the evidence that tight glucose control during hospitalization improves outcomes?

From the Section of Endocrinology, Yale University School of Medicine, New Haven, CT. Address reprint requests to Dr. Inzucchi at the Section of Endocrinology, Yale University School of Medicine, 333 Cedar St., LLCI-101, New Haven, CT 06520-8020, or at silvio.inzucchi@yale.edu.

N Engl J Med 2006;355:1903-11.

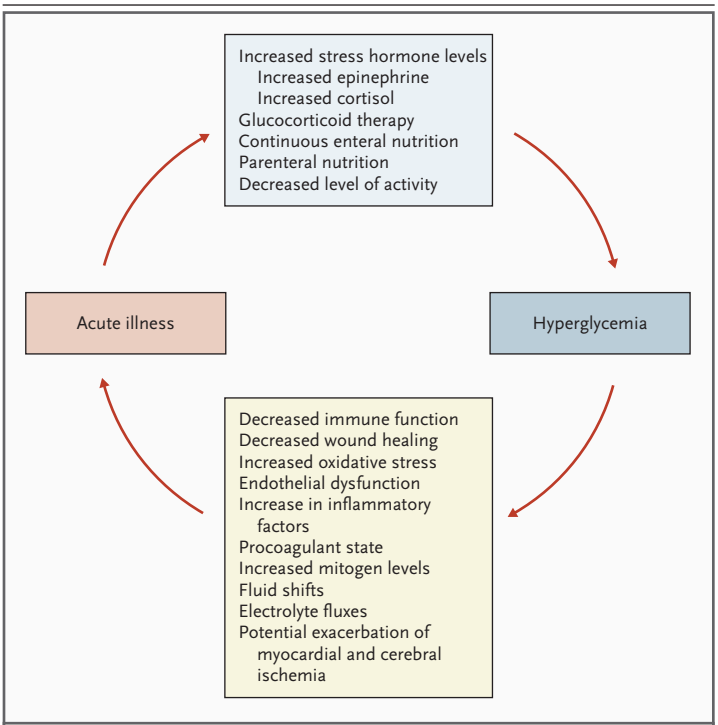


Figure 1. The Relationship between Acute Illness and Hyperglycemia.

STRATEGIES AND EVIDENCE

Several studies have assessed the benefits of aggressive glucose control in the critical care setting, but they have involved markedly different patient populations (patients with and those without diabetes), study designs, glucose targets, and insulin strategies. Moreover, their results have not been uniformly consonant.

In an observational study involving 1499 patients with diabetes in a cardiothoracic ICU, the use of an insulin infusion protocol to lower glucose levels to 150 to 200 mg per deciliter (8.3 to 11.1 mmol per liter) in the 24 hours after open heart surgery, as compared with the use of conventional insulin "sliding scales" in historical controls, was associated with a significant reduction in the incidence of deep sternal wound infection (0.8% vs. 2.0%). The lack of randomization makes these results difficult to interpret, however, since other improvements in care had probably occurred since the period when the controls were treated. However, similar results have been reported in smaller randomized[14] and nonrandomized[15] studies of glucose control after cardiac surgery.

The Diabetes Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study randomly assigned 620 patients with diabetes and acute myocardial infarction to intensive or conventional glucose management both in the hospital and for 3 months after discharge.[16] Intensive management — the use of an insulin infusion for at least the first 24 hours of hospitalization to reduce glucose levels to 126 to 196 mg per deciliter (7.0 to 10.9 mmol per liter), followed by multiple daily injections — resulted in a mean glucose level at 24 hours of 173 mg per deciliter (9.6 mmol per liter), as compared with 211 mg per deciliter (11.7 mmol per liter) among patients assigned to conventional glucose control ($P<0.001$). In the group receiving intensive management, the 1-year mortality rate was 29% lower than that in the group receiving conventional glucose control (18.6% vs. 26.1%, $P=0.03$) and remained significantly lower at 5 years.[17] Because of the study's design, however, it is not known whether the inpatient or outpatient intervention was responsible for the risk reduction. The DIGAMI-2 Study attempted to address this issue by randomly assigning 1253 patients with diabetes to one of three treatments after acute myocardial infarction: aggressive inpatient treatment (insulin infusion; target glucose level, 126 to 180 mg per deciliter [7.0 to 10.0 mmol per liter]) and outpatient treatment, aggressive inpatient treatment only, or conventional care throughout.[18] There were no significant differences in the rates of death or complications among the groups, but the study was statistically underpowered, and there was ultimately little difference in their mean glucose levels. Consequently, little can be concluded from this report or from another similarly flawed study.[19]

Studies involving glucose, insulin, and potassium (GIK) infusions have also had conflicting results.[20] These investigations did not target glucose levels but instead assessed the potential benefit of insulin infusion itself during or immediately after acute myocardial infarction. In the largest of these studies,[21] involving more than 20,000 patients, GIK infusions had no benefit; however, the glucose levels in the treatment group were actually higher than those in the control group.

Nonetheless, there is some rigorous evidence that tight glycemic control in the ICU setting is beneficial. A randomized trial of 1548 intubated patients in the surgical ICU (13% with an established diagnosis of diabetes) compared aggressive treatment with an insulin infusion (target glucose

level, 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with standard care (intravenous insulin administered solely to those with a glucose level exceeding 215 mg per deciliter [11.9 mmol per liter]).[22] The mortality rate was 42% lower (4.6% vs. 8.0%, P<0.04) in the group that received aggressive treatment. This reduction was attributed to effects in patients who remained in the ICU for more than 5 days. Intensively treated patients also had significantly lower rates of dialysis and septicemia, as well as a reduced need for blood transfusion and ventilatory support.

In a subsequent study, involving 1200 patients in the medical ICU and using the same protocol, the results were less clear.[23] Overall, the in-hospital mortality rate (the primary outcome) was not significantly reduced in the intensive-treatment group, as compared with the conventional-treatment group (37.3% vs. 40.0%, P=0.33). Intensive management did, however, result in decreased rates of complications, including a reduced duration of mechanical ventilation, and earlier discharge. In a prespecified subgroup of 767 patients who remained in the ICU for at least 3 days, intensive treatment, as compared with conventional treatment, reduced the in-hospital mortality rate (43.0% vs. 52.5%, P=0.009). However, it was not possible to predict a priori the length of stay, and the mortality rate was increased with intensive treatment among patients whose ICU stay was shorter than 3 days. The increase, although not significant according to the results of proportional-hazards analysis (hazard ratio, 1.09; 95% confidence interval, 0.89 to 1.32), remains a concern.

In both trials, hypoglycemia (defined by a glucose level of less than 40 mg per deciliter [2.2 mmol per liter]) was substantially more common in the intensively treated cohort than in the cohort receiving conventional treatment (5.2% vs. 0.7% in a surgical ICU[22] and 18.7% vs. 3.1% in a medical ICU[23]). Although hypoglycemia was not associated with hemodynamic compromise or seizures in these studies, the general implications of this condition in critically ill patients remain unknown. Moreover, in the medical ICU trial, hypoglycemia was an independent predictor of the risk of death.

A more conservative approach to intensive management was investigated in a mixed medical–surgical ICU, in which insulin was administered subcutaneously to obtain a target glucose level below 140 mg per deciliter (7.8 mmol per liter). Insulin was infused only if the glucose level exceeded 200 mg per deciliter.[24] The in-hospital mortality rate was significantly lower among patients receiving intensive treatment than among historical controls (14.8% vs. 20.9%, P=0.002). No data are available from clinical trials of aggressive inpatient glucose control outside the ICU.

FACTORS AFFECTING TREATMENT STRATEGIES

Insulin resistance and insulin secretory capacity in hospitalized patients are affected by numerous factors, including the severity of illness and medications (in particular, glucocorticoids and pressors); in addition, a patient's diet is often unpredictable in the hospital, and tests and procedures frequently interrupt both meal and medication schedules, further complicating the management of glucose levels.[3,4,25] It is important to know whether a patient has a history of diabetes and, if so, the type (since patients with type 1 diabetes have an increased risk of ketosis), as well as the regimen used to control glucose levels before hospitalization. Also important is the patient's nutritional status (which will determine the need for basal or prandial insulin) and prevailing glucose level (which will guide decisions about the aggressiveness of the initial regimen and the pace at which it is advanced). Determining whether aggressive glucose control is practical will depend in part on the expected course of treatment during hospitalization and in part on the anticipated length of stay. Decisions regarding inpatient glucose control will also be influenced by the quality of the patient's control before admission. In those with established diabetes, a glycated hemoglobin test will provide a rapid assessment of control on the outpatient regimen. Such information will help guide the need for more intensive efforts. In patients with new hyperglycemia — that is, without a previously established diagnosis of diabetes — an elevated glycated hemoglobin value, especially one above 7%, suggests the presence of diabetes before admission.

ORAL AGENTS

Insulin is generally the preferred form of treatment for inpatients because the dose can be titrated more rapidly than the dose of oral agents and it does not have a dose ceiling. However, in selected patients, particularly patients who are not critically ill, whose condition is well controlled, and who are expect-

ed to eat normally, it is reasonable to continue oral therapies if they were working well before admission. Particular attention is warranted for patients taking metformin, given the contraindications to its use (including renal impairment, heart failure, and the need for radiographic contrast studies). Thiazolidinediones should be stopped if heart failure or liver-function abnormalities are present. (Even after discontinuation, the antihyperglycemic effects of this class of drugs may persist for several weeks.) In patients who are not eating regularly, the insulin secretagogues (e.g., sulfonylureas) are particularly dangerous and α-glucosidase inhibitors are ineffective. Modest reductions in the doses of oral agents can be considered in hospitalized patients on calorie-restricted diets, because such diets may result in improved glucose control. If the glucose level is notably elevated on admission, or if glucose control deteriorates in the hospital — both frequent phenomena — insulin therapy should be initiated.

Figure 2 (facing page). Proposed Algorithm for the Management of Diabetes and Hyperglycemia in the Noncritical Care Setting.

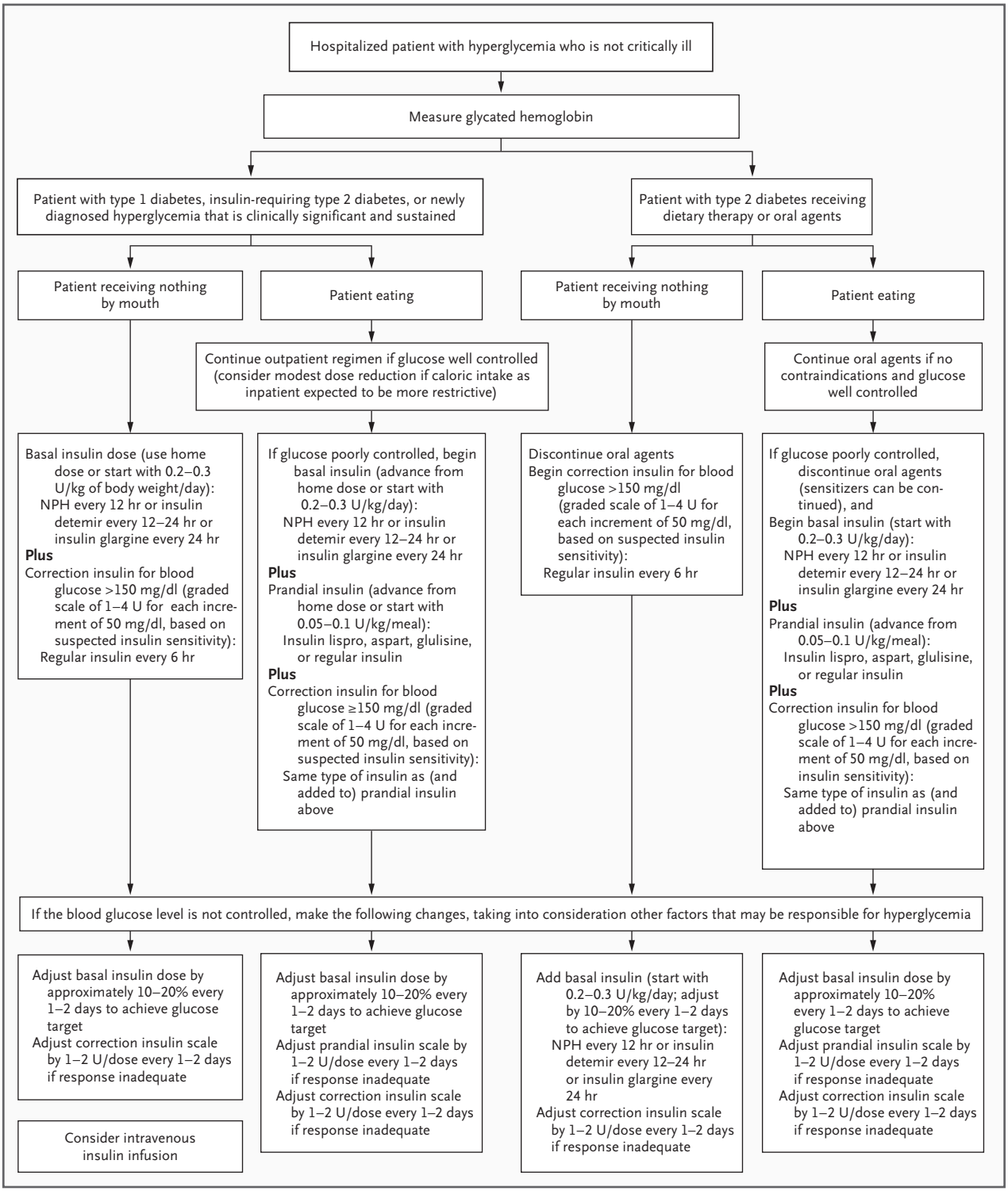
A preprandial glucose target of 90 to 150 mg per deciliter is recommended for most patients. Suggested doses are approximations; actual doses will depend on the degree of hyperglycemia, the patient's insulin sensitivity and nutritional status, and the severity of the underlying illness. Ongoing monitoring of the response to treatment will best guide further dose adjustments, which should take into account the various factors that affect glucose levels in the hospital setting, including any mistiming of glucose measurement, meal intake, or insulin administration. Aggressiveness should also be guided by practical factors, such as the trajectory of the patient's recovery, the expected duration of the hospitalization, the monitoring capacities in the hospital ward, the ability of the patient to perceive hypoglycemia, and the clinician's assessment of the value of urgent glucose control to the individual patient's acute illness.

INSULIN

In the ICU, insulin is usually administered by continuous intravenous infusion; optimally, a standardized algorithm is followed. Several validated protocols are available.[3,22,26-30] The most effective are those that use dynamic scales, incorporating the rate of change in glucose into dose adjustments.[29,31] (An example of a validated protocol, adapted from Goldberg and Roussel,[29] is provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Frequent monitoring of glucose levels (usually hourly) is imperative to minimize the risk of hypoglycemia. As the patient's clinical status improves, the transition to subcutaneous insulin can be made, with the use of the most recent infusion rate to approximate the overall daily requirement, dividing this into basal and prandial components (Fig. 2). Also, proper overlap between intravenous and subcutaneous insulin must be ensured, especially in patients with type 1 diabetes. Patients with type 2 diabetes who require less than 2 U of insulin per hour may do well with less intensive regimens; oral agents may be sufficient in some patients.

Outside the critical care setting, sliding scales are still commonly used to provide insulin in a graded fashion in response to established hyperglycemia.[4] The use of this strategy alone is generally inappropriate, however,[32] especially in patients with type 1 diabetes, who require basal insulin replacement to suppress ketogenesis. Anticipatory strategies for dosing insulin result in superior control. Therapies that involve some basal (i.e., intermediate to long-acting) insulin, with short- or rapid-acting insulin provided before meals to blunt postprandial spikes in glucose (mealtime, or prandial, bolus), provide results that most closely resemble physiologic patterns of glucose control.[3,33-35] Rapid-acting insulin analogues (lispro, aspart, and glulisine) should be given immediately before a meal. A prudent approach is to provide the insulin only when the meal tray is in front of the patient. Regular human insulin should ideally be given 30 minutes before meals — a goal that may be difficult to meet in the busy hospital setting. Also, the rapid-acting analogues provide better postprandial control. In patients whose dietary intake is uncertain, prandial insulin dosing should be conservative. One alternative is to allow a rapid-acting insulin analogue to be administered immediately after a meal, on the basis of the amount the patient actually consumed.

Adjustable supplementary doses ("correction" insulin) of identical type may be combined with the prandial insulin to compensate for premeal hyperglycemia. Insulin-sensitive patients (most patients with type 1 diabetes, lean persons, those receiving relatively low total daily doses of insulin [<30 to 40 U per day], or those prone to hypoglycemia) will require only modest doses (e.g., 1 U to correct blood glucose levels of 150 mg per deciliter [8.3 mmol per liter], 2 U to correct levels of 200 mg per deciliter [11.1 mmol per liter], and so on).



Most patients with type 2 diabetes (those who are overweight or who are receiving moderate doses of insulin [40 to 100 U per day]) will require moderate correction doses (e.g., 2 U to correct blood glucose levels of 150 mg per deciliter, 4 U to correct levels of 200 mg per deciliter, and so on). Some patients with type 2 diabetes and severe insulin resistance (those who are very obese, those receiving large amounts of insulin [>100 U per day], or those taking corticosteroids) may require large corrective doses (e.g., 4 U for blood glucose levels of 150 mg per deciliter, 8 U for levels of 200 mg per deciliter, and so on). Insulin sensitivity may change rapidly as the underlying illness improves.

As a general rule, in patients in whom diabetes is well controlled, the ratio of the doses of total daily basal insulin to prandial insulin is about 1:1. The basal insulin dose is adjusted depending on the overall glucose profile. If glargine or detemir is used, the dose adjustment should be based on the morning fasting blood glucose level. If NPH is used, the dose adjustment should be based on the morning fasting blood glucose level or the blood glucose level measured before the evening meal. During the titration phase, it is also acceptable to incorporate the correction dose into the basal insulin dose prospectively, by carefully adding 50% of the total amount of the correction dose administered the day before into the next day's basal insulin order. Adjustments of prandial insulin doses are based on the level of postprandial glycemia, as reflected by the blood glucose level measured before the midday meal and at bedtime. The correction insulin dose may be adjusted after an assessment of the patient's response to prior doses. To ensure patient safety, insulin requirements should be reassessed immediately after any change in nutritional status.

Some patients with type 2 diabetes may have a response to less aggressive insulin strategies, such as basal insulin alone (e.g., glargine once daily, detemir once or twice daily, or NPH twice daily) or convenient premixed formulations involving intermediate and short- or rapid-acting insulins (e.g., "70/30"). These strategies may be acceptable for those with hyperglycemia that is not severe, especially if discharge is imminent and there is no time for titration of more complex regimens.

In insulin-treated patients who are not eating, basal insulin should be provided, with regular insulin administered every 6 hours as necessary. This is mandatory in patients with type 1 diabetes and advisable in patients with type 2 diabetes. (Insulin infusion can also be used in this setting, or if the adequacy of subcutaneous absorption is in doubt.)

In insulin-treated patients who are eating, the regimen used before hospitalization can be continued if it was successful and if the glucose level is acceptable on admission. As with oral agents, depending on the clinical circumstances, modest dose reductions, particularly for patients with type 2 diabetes, should be considered because of the anticipated reduction in caloric intake. If the glucose level is high on admission (more than 200 mg per deciliter), the insulin dose should generally be increased. A change to a basal-prandial-correction strategy should be considered. Intravenous infusions of insulin should be considered if marked hyperglycemia (glucose levels of 300 to 400 mg per deciliter [16.7 to 22.2 mmol per liter] or more) persists for more than 24 hours and is not controlled by increasing the dose of subcutaneous insulin. Intravenous insulin works rapidly, and the dose can be titrated more precisely than can the dose of subcutaneous injections. Also, because intravenous insulin has a very short half-life (5 to 9 minutes), hypoglycemia, if it occurs, can be quickly reversed. For safety reasons, a higher glycemic target than is used in ICUs is advisable when insulin infusions are used on general wards. Adequate nursing resources are needed for safe monitoring and titration.

The glucose levels in patients receiving continuous enteral tube feeding are optimally managed mainly with the use of basal insulin, with correction doses of regular insulin added as needed every 6 hours. If feeding is interrupted, an amount of carbohydrate (i.e., dextrose) similar to that being used enterally should be administered intravenously to prevent hypoglycemia. For patients receiving total parenteral nutrition, regular insulin can be added to the intravenous bags; the dose is gradually titrated in increments of 5 to 10 U per liter to achieve glycemic control.

Close monitoring of glucose levels is needed, regardless of the insulin regimen, with frequent adjustments made (as often as every 1 to 2 days) to optimize control. Before doses are increased, however, it is important to consider factors that may contribute to hyperglycemia (e.g., missed doses,

excess snacking, or new infection) and to address them. The mistiming of glucose measurement (in a finger-stick blood sample), meal ingestion, and prandial insulin administration is another frequent culprit of glycemic lability in the hospital. Proper coordination between dietary and nursing services is mandatory for quality inpatient glucose management. Ideally, finger sticks should always be performed before meals and at bedtime. Early postprandial (i.e., within 2 to 3 hours after the last meal) blood glucose checks may lead to overly aggressive insulin coverage and should generally be avoided except in specific circumstances, such as in the management of diabetes in pregnant women.

Before the patient is discharged, the insulin regimen may need to be simplified, depending on the capacities of the patient. Once-daily, long-acting insulin alone is practical in some patients with type 2 diabetes. In others, who have required little insulin in the hospital or whose control has been excellent when receiving less than 25 to 30 U per day, diet therapy or oral agents may eventually be adequate. Follow-up is warranted within 1 to 2 weeks after discharge if treatment with antihyperglycemic medications was initiated or stopped or if the dose was changed during hospitalization.

Similar recommendations apply to hospitalized patients with newly diagnosed hyperglycemia, although some patients may no longer require glucose-lowering therapy after they have recovered from acute illness. Fasting glucose levels (and perhaps glycated hemoglobin values) should be reassessed 1 to 2 months after discharge in these patients.

GUIDELINES

Two published consensus statements[2,36] provide recommendations for glucose targets in hospitalized patients (Table 1). These statements remain controversial, because they extrapolate data from the few randomized trials involving critically ill patients to the general population of hospitalized patients. There is general agreement that insulin should be administered by intravenous infusion in the ICU and that other insulin regimens should be as similar to physiologic patterns as possible, particularly in patients with type 1 diabetes.[1-4,25] In the absence of trials assessing the efficacy of any particular subcutaneous insulin strategy in the hospital, recommendations are based largely on clinical experience.

Table 1. Recommended Target Blood Glucose Levels for Hospitalized Patients.*

Location	American Diabetes Association[36]	American College of Endocrinology[2]
ICU	As close to 110 mg/dl as possible; generally <180 mg/dl	<110 mg/dl
General ward	As close to 90–130 mg/dl as possible; <180 mg/dl postprandial	<110 mg/dl before a meal; maximal <180 mg/dl

* The author believes these targets may be too stringent, on the basis of the available evidence. To convert values for glucose to millimoles per liter, multiply by 0.05551.

AREAS OF UNCERTAINTY

Data on the role of tight glycemic control in hospitalized patients remain limited. Although most studies suggest that reducing glucose levels in critically ill patients improves outcomes,[37] the precise target, the optimal mode of insulin administration, and the patients most likely to benefit (as well as the way to identify them) remain unknown.[38,39] The finding that intensive glucose control reduces the risk of death mainly among patients with extended ICU stays suggests that not all critically ill patients have a similar response to glucose control.[22,23,40] Ongoing trials of intensive insulin therapy in the ICU are expected to provide additional information.[41]

The optimal management of glycemia immediately after acute myocardial infarction is highly uncertain.[14-17,42] Of concern are two recent observational studies that demonstrated an association between the development of hypoglycemia during admission for acute myocardial infarction and an increased risk of death.[43,44] Although the results of some studies suggested that insulin therapy may confer benefits other than lowering glucose levels in patients with acute coronary syndromes (e.g., antilipolytic, vasodilatory, anti-inflammatory, and profibrinolytic effects),[45] the clinical relevance of these effects is unclear, and other available data[21] argue against the idea that insulin plays a therapeutic role outside of glucose control.

It is unknown whether the benefits of inten-

sive insulin therapy demonstrated in some ICU studies extend to patients who are not critically ill. Hospital wards are less well staffed than ICUs and may lack adequate resources for more intensive monitoring. The balance between the potential benefits and risks (of hypoglycemia, in particular) must be carefully assessed. Patients with impaired mental status and decreased capacity to both perceive and respond to low glucose levels are of particular concern.[46]

CONCLUSIONS AND RECOMMENDATIONS

In surgical and medical ICUs, blood glucose levels should probably be maintained below 140 mg per deciliter[24,39] and perhaps even below 110 mg per deciliter,[22,23] but more information is needed on which patients are most likely to benefit. The optimal glucose range for patients in the coronary care unit is more debatable; a reasonable goal may be higher (up to 180 mg per deciliter).[15] Intravenous infusion of insulin allows for more rapid titration (and more reliable absorption) in critically ill patients than does subcutaneous injection, and I would use this approach in the patient described in the vignette, aiming for a plasma glucose level in the range of 90 to 120 mg per deciliter. Although data from trials of glucose control in medical and surgical inpatients who are not critically ill are lacking, my approach is to aim for premeal targets of 90 to 150 mg per deciliter (5.0 to 8.3 mmol per liter)[39] not only to circumvent concern about hyperglycemia but also to minimize the risk of hypoglycemia. Importantly, rigorous glycemic control and monitoring in the hospital setting require supervision by a knowledgeable, trained staff.

Although the precise glucose targets for hospitalized patients remain controversial,[1-3,38,39] having a precise target may be less important than recognizing that diabetes should not be ignored during hospitalization; that insulin therapy, when possible, should be proactive, with frequent adjustments to optimize control; that insulin infusions should be used when necessary; and that the transition to outpatient care should involve patient education and the use of a manageable regimen on discharge.[47]

Dr. Inzucchi reports having received research support from Eli Lilly. No other potential conflict of interest relevant to this article was reported.

I thank Dr. Philip Goldberg for his advice during the preparation of this manuscript.

REFERENCES

1. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004;27:553-91. [Errata, Diabetes Care 2004;27:856, 1255.]
2. Garber AJ, Moghissi ES, Bransome ED Jr, et al. American College of Endocrinology position statement on inpatient diabetes and metabolic control. Endocr Pract 2004;10:77-82.
3. 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;88:2430-7.
4. Metchick LN, Petit WA Jr, Inzucchi SE. Inpatient management of diabetes mellitus. Am J Med 2002;113:317-23.
5. 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;63:356-61.
6. Golden SH, Peart-Vigilance C, Kao WHL, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care 1999;22:1408-14.
7. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation 1999;99:2626-32.
8. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78:1471-8.
9. 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.
10. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773-8.
11. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-32.
12. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005;111:3078-86.
13. 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;87:978-82.
14. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497-502.
15. Hruska LA, Smith JM, Hendy MP, Fritz VL, McAdams S. Continuous insulin infusion reduces infectious complications in diabetics following coronary surgery. J Card Surg 2005;20:403-7.
16. Malmberg K, Ryden 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.
17. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. BMJ 1997;314:1512-5.
18. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of in-

sulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650-61.
19. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 2006;29:765-70.
20. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 1997;96:1152-6.
21. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA 2005;293:437-46.
22. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359-67.
23. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354: 449-61.
24. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004;79:992-1000. [Erratum, Mayo Clin Proc 2005;80:1101.]
25. Moghissi ES, Hirsch IB. Hospital management of diabetes. Endocrinol Metab Clin North Am 2005;34:99-116.
26. 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;125:1007-21.
27. Markovitz LJ, Wiechmann RJ, Harris N, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. Endocr Pract 2002;8:10-8.
28. Goldberg PA, Siegel MD, Sherwin RS, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. Diabetes Care 2004; 27:461-7.
29. Goldberg PA, Roussel MG, Inzucchi SE. Clinical results of an updated insulin infusion protocol in critically ill patients. Diabetes Spectrum 2005;18:188-91.
30. Ku SY, Sayre CA, Hirsch IB, Kelly JL. New insulin infusion protocol improves blood glucose control in hospitalized patients without increasing hypoglycemia. Jt Comm J Qual Patient Saf 2005;31:141-7.
31. Meijering S, Corstjens A, Tulleken JE, Meertens JHJM, Zijlstra JG, Ligtenberg JM. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. Crit Care 2006;10:R19.
32. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Arch Intern Med 1997;157:545-52.
33. Hirsch IB. Insulin analogues. N Engl J Med 2005;352:174-83.
34. Riddle MC. Glycemic management of type 2 diabetes: an emerging strategy with oral agents, insulins, and combinations. Endocrinol Metab Clin North Am 2005;34:77-98.
35. Edelman SV, Morello CM. Strategies for insulin therapy in type 2 diabetes. South Med J 2005;98:363-71.
36. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2005;28:Suppl 1:S4-S36. [Erratum, Diabetes Care 2005;28:990.]
37. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. Arch Intern Med 2004; 164:2005-11.
38. Bryer-Ash M, Garber AJ. Point: inpatient glucose management: the emperor finally has clothes. Diabetes Care 2005; 28:973-5.
39. Inzucchi SE, Rosenstock J. Counterpoint: inpatient glucose management: a premature call to arms? Diabetes Care 2005;28:976-9.
40. Falciglia M, D'Alessio DA, Almenoff PLMD, Freyberg RW, Diab D, Render ML. Hyperglycemia and mortality in 252,000 critically ill patients. Presented at the 66th Scientific Sessions of the American Diabetes Association, Washington, DC, June 9–13, 2006. abstract.
41. ClinicalTrials.gov. Normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation (NICE-SUGAR study). (Accessed October 6, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00220987.)
42. 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. Ann Thorac Surg 1999;67:352-62.
43. Pinto DS, Skolnick AH, Kirtane AJ, et al. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2005; 46:178-80.
44. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005;26:1255-61.
45. Chaudhuri A, Janicke D, Wilson MF, et al. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment-elevation myocardial infarction. Circulation 2004;109:849-54.
46. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of the critically ill? Diabetologia 2006;49: 1722-5.
47. Inpatient diabetes and glycemic control: management: a call to action conference, January 2006. AACE-ADA Consensus Development Conference position statement. (Accessed October 6, 2006, at http://www.aace.com/meetings/consensus/IIDC/.)