



## Improving glycemic control in hospital patients with and without diabetes mellitus


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Articles based on the proceedings of a symposium held December 4 and 6, 2006, during the ASHP Midyear Clinical Meeting in Anaheim, CA, and supported by an educational grant from Eli Lilly and Company.

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# Improving glycemic control in hospital patients with and without diabetes mellitus

## Introduction

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*Am J Health-Syst Pharm* 2007; 64(Suppl 6):S3

**H**yperglycemia in hospitalized patients with and without diabetes has been the focus of recent attention because it increases morbidity, mortality, and costs.<sup>1</sup> Hyperglycemia causes problems with tissue and organ perfusion and wound healing, and it increases the risk for bacterial infection, especially in patients with venous catheters or who have recently undergone surgery.<sup>1</sup>

Previously undiagnosed diabetes and impaired glucose tolerance are common in hospitalized patients.<sup>2</sup> Blood glucose concentrations at the time of hospital admission can serve as markers for adverse outcomes in hospital patients.

The use of nationally standardized measures for assessing the quality of blood glucose manage-

ment in hospitalized patients has been advocated.<sup>3,4</sup> In the future, hospital accreditation may hinge on normalizing average blood glucose concentrations in hospital patients. Frequent bedside blood glucose monitoring plays a key role in lowering blood glucose concentrations, and continuous monitoring may be feasible in the future.<sup>4</sup>

The first article in this supplement discusses the etiology and impact on outcomes of hyperglycemia in hospitalized patients. The approach to managing hyperglycemia in the hospital setting is described in detail in the second article. Finally, the development, implementation, and cost justification of hospital protocols for hyperglycemia management are addressed in the third article.

### References

1. Clement S, Braithwaite SS, Magee MF et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; 27:553-91.
2. Norhammar A, Tenerz A, Nilsson G et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; 359:2140-4.
3. Goldberg PA, Bozzo JE, Prem GT et al. "Glucometrics"—assessing the quality of inpatient glucose management. *Diabetes Technol Ther* 2003; 8:560-9.
4. ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control: a call to action. *Diabetes Care* 2003; 29:1955-62.

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Based on the proceedings of a symposium held December 4 and 6, 2006, during the ASHP Midyear Clinical Meeting, Anaheim, CA, and supported by an educational grant from Eli Lilly and Company. Dr. Campbell received an honorarium for his participation in the

symposium and for the preparation of this article. Dr. Campbell reports that he has no affiliation with or financial interest in a commercial organization that pose a conflict of interest with this article.

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DOI 10.2146/ajhp070099

# Etiology and effect on outcomes of hyperglycemia in hospitalized patients

R. KEITH CAMPBELL

An estimated 20.8 million Americans (7% of the U.S. population) have diabetes, including 14.6 million patients who have been diagnosed and 6.2 million people who are undiagnosed.<sup>1</sup> The majority (90-95%) of patients have type 2 disease; type 1 disease affects only 5-10% of patients.<sup>1</sup> In 2005, 1.5 million new cases of diabetes mellitus were diagnosed among adults 20 years of age or older. More than 41 million Americans have pre-diabetes (i.e., impaired fasting glucose or impaired glucose tolerance).<sup>1</sup> Exercise and diet prevent the progression to diabetes in roughly 60% of patients with prediabetes.<sup>2</sup>

In 2002, the direct and indirect costs of diabetes amounted to \$132 billion in the U.S.<sup>3</sup> The largest component (\$40 billion) was hospital costs. The hospital costs for patients with diabetes were about 2.1 times higher than expenditures for people without diabetes.<sup>3</sup>

The prevalence of diabetes is increasing in the U.S., but glycemic control appears to be deteriorating.<sup>4,5</sup> Poor glycemic control is associated with macrovascular and microvascular complications.<sup>6</sup>

**Purpose.** The prevalence of diabetes in U.S. hospitals, etiology and pathophysiology of hyperglycemia in hospitalized patients, impact of hyperglycemia on patient outcomes, and benefits of hyperglycemia correction are described.

**Summary.** Diabetes mellitus is a common and costly condition with an increasing prevalence in the U.S. Hyperglycemia is common among hospital patients with and without diabetes. Possible causes of hyperglycemia include illness-related metabolic stress, parenteral nutrition, and pharmacotherapy. The deposition of advanced glycosylation end products, capillary basement membrane thickening, impaired immune function, oxidative stress, impaired lipid metabolism, prothrombotic changes, activation of protein kinase C- $\beta$ , vascular leakage, capillary non perfusion, and induction of vascular endothelial growth factor are among the harmful effects of hyperglyce-

mia. In various types of patients and hospital settings, hyperglycemia increases the mortality rate, risk of postoperative nosocomial infection, need for intensive care unit admission, length of hospital stay, and hospital charges. The benefits of using intensive therapy to correct hyperglycemia in hospitalized patients in reducing mortality and the risk of infections and other adverse outcomes are well documented.

**Conclusion.** Efforts are needed to manage hyperglycemia in hospitalized patients with and without diabetes to minimize the morbidity, mortality, and costs associated with hyperglycemia.

**Index terms:** Diabetes mellitus; Economics; Epidemiology; Hospitals; Hyperglycemia; Mortality; Nutrition; Outcomes; Patient care; Toxicity

**Am J Health-Syst Pharm.** 2007; 64(Suppl 6):S4-8

An accurate estimate of the number of patients admitted to hospitals with diabetes is difficult to make because type 2 diabetes is underdiagnosed.<sup>7</sup> A conservative estimate of the prevalence of diabetes in hospitalized adult patients is 12.4-25%.<sup>7</sup>

For every two patients with diabetes in the hospital, there is thought to be at least one other patient in the hospital with unrecognized diabetes who is at risk for poor outcomes.<sup>8-10</sup> In 2000, 12.4% of discharges from U.S. listed diabetes as the diagnosis.<sup>7</sup>

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DOI 10.2146/ajhp070100

## Etiology

Hyperglycemia in hospitalized patients may have various causes, including illness-related metabolic stress, poor management of blood glucose concentrations, parenteral nutrition, and drugs (e.g., thiazide diuretics,  $\beta$ -blockers, vasopressors, atypical antipsychotic agents, protease inhibitors, and glucocorticoids).<sup>7,11-14</sup> Metabolic stress during critical illness causes the release of counterregulatory hormones (e.g., epinephrine, cortisol), insulin resistance, and hyperglycemia.<sup>7,15</sup> Parenteral nutrition increases the risk of hyperglycemia in patients with and without diabetes, especially when the infusion rate is rapid or the patient is elderly.<sup>12,13</sup>

Various drug therapies can cause hyperglycemia. Glucocorticoids increase hepatic glucose production, decrease glucose uptake by muscle tissue, and cause insulin resistance.<sup>7,14</sup>

## Pathophysiology

In the past, clinicians were more concerned about the risk of hypoglycemia than hyperglycemia in hospitalized patients, although most episodes of hypoglycemia in a hospital setting are mild, transient, and readily treated.<sup>10</sup> Short-term hyperglycemia in hospitalized patients with diabetes is associated with dehydration, electrolyte imbalance, ketoacidosis, cognitive impairment, macrovascular and microvascular damage, slowed healing and oxidative stress, which causes cell and tissue injury.<sup>7,15</sup> The long-term effects of hyperglycemia are listed in Table 1. Hyperglycemia causes the deposition of advanced glycosylation end products (AGEs) on vascular walls, resulting in capillary basement membrane thickening and microvascular complications. Hemoglobin A1C is one such AGE that is useful for monitoring long-term glycemic control in patients with diabetes. Reactive oxygen species and aldose reductase cause oxidative stress and

Table 1.

### Harmful Effects of Hyperglycemia<sup>8,16,17</sup>

- Capillary basement membrane thickening
- Impaired phagocytosis and ability to fight infections
- Abnormally high levels of advanced glycosylated end products
- $\uparrow$  aldose reductase levels and glucose metabolism to sorbitol
- Oxidative stress
- Abnormal lipid metabolism
  - hypercholesterolemia
  - hypertriglyceridemia -  $\uparrow$  lipoprotein (a)
- $\downarrow$  vascular contractility
- $\uparrow$  blood pressure
- $\uparrow$  platelet adhesiveness
- $\uparrow$  blood viscosity
- $\downarrow$  erythrocyte flexibility
- $\uparrow$  serum fibrinogen levels
- $\uparrow$  tissue plasminogen activator inhibitor-1 levels
- $\uparrow$  levels of coagulation factors (factor VII, von Willebrand factor)
- $\uparrow$  C-reactive protein levels
  - $\uparrow$  activation of some isoforms of protein kinase C

contribute to microvascular complications.<sup>7</sup> According to the aldose reductase theory (also known as the polyol pathway), glucose is metabolized to sorbitol by aldose reductase, levels of which are increased by hyperglycemia.<sup>16</sup> High sorbitol levels are associated with cataracts and nerve damage. Sugar-free sweeteners and candy that contain sorbitol are not particularly harmful to people with diabetes because they contain small amounts of sorbitol.

Hyperglycemia also causes immune system dysfunction (e.g., impaired phagocytosis), which makes patients vulnerable to infections.<sup>7</sup> Migration of white blood cells through capillary basement membranes is impeded when the membranes are thickened, thereby reducing the ability to fight infection. Hyperglycemia also is accompanied by an increase in inflammatory cytokines and C-reactive protein.

Hyperglycemia can reduce vascular contractility and cause hypertension.<sup>7</sup> It also can cause abnormal lipid metabolism, resulting in hypercholesterolemia, hypertriglyceridemia, and atherosclerosis. Various hemorrheologic factors are adversely

affected by hyperglycemia, including platelet adhesiveness, blood viscosity, and erythrocyte flexibility. Serum fibrinogen, tissue plasminogen activator inhibitor-1, and several clotting factors are increased by hyperglycemia. These changes predispose to thrombosis, vascular occlusion, and macrovascular complications, particularly coronary heart disease.

Activation of protein kinase C- $\beta$  (PKC- $\beta$ ) can occur as a result of hyperglycemia, and PKC- $\beta$  activation has been linked to microvascular dysfunction, with increased vascular permeability, reduced perfusion, and leukocyte adhesion.<sup>16</sup> In the eye, PKC- $\beta$  activation leads to vascular leakage, macular edema, capillary non perfusion, and induction of growth factors, particularly vascular endothelial growth factor (VEGF).<sup>16</sup> Proliferative diabetic retinopathy with macular edema is a major cause of vision loss, and a substantial amount of the retinal neovascularization and excessive vascular permeability are mediated by VEGF.<sup>17</sup> Selective inhibitors of PKC- $\beta$  (e.g., ruboxistaurin) are under investigation for the prevention and treatment of proliferative and nonprolif-

erative diabetic retinopathy, diabetic macular edema, nephropathy, and peripheral neuropathy. Such therapies address the underlying cause rather than the symptoms of these disorders. The results obtained to date with ruboxistaurin have been promising.<sup>18</sup>

Increased body weight, dental caries, gum disease, depression, and hearing disorders are among the harmful effects of hyperglycemia. Maternal hyperglycemia can result in neonatal morbidity and mortality.<sup>19</sup> The many harmful effects of hyperglycemia provide the rationale for intensive glycemic control.

### Impact of hyperglycemia on outcomes

The adverse effects of hyperglycemia on patient outcomes have been documented in a variety of hospital settings and types of patients, including general medical and surgical patients, patients with acute myocardial infarction, patients undergoing cardiac surgery, and patients with stroke.<sup>9,20-24</sup>

In a retrospective analysis of blood glucose concentrations in a heterogeneous group of 1826 critically ill patients in an intensive care unit (ICU), the hospital mortality rate increased progressively with increases in the average blood glucose concentration.<sup>20</sup> The average blood glucose values were significantly higher among non-survivors than among survivors.

A retrospective review of the records for 2030 adults admitted to a community teaching hospital found that 38% of the patients had hyperglycemia (defined as a fasting glucose concentration of at least 126 mg/dL or a random blood glucose concentration of at least 200 mg/dL on two or more occasions) at the time of admission or during hospitalization.<sup>9</sup> Twenty-six percent of patients had a history of diabetes, and 12% of patients had no such history. Newly detected hyperglycemia was associated

with a longer length of hospital stay, higher rate of ICU admission, lower likelihood of discharge to home, and greater need for transitional or nursing home care compared with patients with a history of diabetes or normoglycemia. Hyperglycemia was an independent marker of inpatient mortality in patients with newly detected hyperglycemia. The inpatient mortality rate was 16% in patients with newly detected hyperglycemia, 3% in patients with a history of diabetes, and 1.7% in patients with normoglycemia.

A prospective analysis of 100 initially uninfected diabetic patients who underwent elective surgery at a large tertiary care hospital revealed that the rate of postoperative nosocomial infection was 2.7 times higher in patients with early postoperative hyperglycemia (i.e., a blood glucose concentration >220 mg/dL on the first postoperative day) than in patients with lower postoperative blood glucose concentrations.<sup>21</sup> Early postoperative hyperglycemia increased the rate of serious postoperative nosocomial infection (i.e., infections other than urinary tract infection or other minor infections) 5.7 fold.

A meta-analysis was conducted of 15 studies of in-hospital mortality or rates of congestive heart failure after myocardial infarction and blood glucose concentrations at the time of admission of patients with and without diabetes.<sup>22</sup> Hyperglycemia increased the risk of in-hospital mortality 3.9 fold in patients with diabetes and 1.7 fold in patients without diabetes. Hyperglycemia also increased the risk of congestive heart failure and cardiogenic shock in patients without diabetes.

An analysis of perioperative blood glucose concentrations in 1574 patients undergoing coronary artery bypass grafting between 1998 and 1999, including 545 patients with diabetes, revealed that every 50-mg/dL increase in blood glucose concentration was associated with a

37% increase in mortality and a 23% increase in infection rate, differences that are not significant.<sup>23</sup> Significant increases in postoperative hospital length of stay by 0.76 days, hospital charges by \$2824, and hospital costs by \$1769 were associated with each 50-mg/dL increase in blood glucose concentration.

In a retrospective study of 656 patients with ischemic stroke some of whom had a history of diabetes, hyperglycemia (defined as a blood glucose concentration of 130 mg/dL or higher) was associated with a significant increase in 30-day mortality by 87% compared with normoglycemia.<sup>24</sup> Hyperglycemia also significantly increased the hospital length of stay and inpatient hospital charges.

### Benefits of hyperglycemia management

The benefits of intensive therapy to correct hyperglycemia in hospitalized patients are well documented. In an ongoing 17-year, prospective, nonrandomized, interventional study of 4864 patients with diabetes who underwent an open-heart surgical procedure, continuous intravenous insulin therapy significantly reduced the rate of mortality by 57% and the incidence of deep sternal wound infections by 66% to the incidence observed in patients without diabetes.<sup>25</sup> Target blood glucose levels of less than 150 mg/dL and a 3-day postoperative duration of insulin therapy were associated with these benefits. Cardiac-related mortality was significantly higher for patients with postoperative blood glucose concentrations greater than 175 mg/dL than for patients with concentrations less than 150 mg/dL.<sup>26</sup>

In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study (a randomized study known as DIGAMI) of 620 patients with diabetes and acute myocardial infarction, a significant reduction in mortality by 28% was

observed after an average follow up of 3.4 years with intensive glycemic control using insulin-glucose infusion for at least 24 hours followed by subcutaneous insulin injections four times daily compared with standard treatment.<sup>27</sup> The reduction in mortality risk was even greater (51%) in a subset of 272 patients who were at low cardiovascular risk and not previously receiving insulin.

In a prospective, randomized, controlled study of 1548 critically ill adults who were receiving mechanical ventilation in a surgical intensive care unit (SICU), intensive insulin therapy (maintenance of a blood glucose concentration of 80-110 mg/dL while in the SICU and 180-200 mg/dL after SICU discharge) was compared with conventional treatment (infusion of insulin only if the blood glucose concentration exceeded 215 mg/dL, and maintenance of a blood glucose concentration of 180-200 mg/dL).<sup>28,29</sup> Compared with conventional treatment, intensive insulin therapy significantly reduced SICU mortality by 43% (from 8.0% to 4.6%) and overall in-hospital mortality by 34% (from 10.9% to 7.2%).<sup>28</sup> The in-hospital mortality rate was significantly lower in patients with an average blood glucose concentration less than 110 mg/dL compared with patients whose average blood glucose concentration was between 110 mg/dL and 150 mg/dL.<sup>29</sup> Intensive insulin therapy also reduced blood infections by 46%, the incidence acute renal failure requiring dialysis or hemofiltration by 41%, the number of red blood cell transfusions by 50%, and the incidence of critical-illness polyneuropathy by 44% compared with conventional treatment.<sup>28</sup>

Hospital mortality and ICU length of stay were compared before and after implementation of an intensive glucose management protocol in two heterogeneous groups of 800 critically ill, adult, medical-surgical ICU patients.<sup>30</sup> The protocol was designed to maintain plasma glucose values

lower than 140 mg/dL. Continuous i.v. insulin was provided if glucose values exceeded 200 mg/dL on two successive occasions. The protocol significantly reduced hospital mortality by 29% and ICU length of stay by 11%.

Intensive treatment of hyperglycemia was compared with a standard regimen in a small prospective study of 61 ICU patients with a blood glucose concentration exceeding 140 mg/dL.<sup>31</sup> The rate of nosocomial infections was significantly higher in patients receiving the standard insulin regimen than in patients receiving intensive insulin treatment. Compared with the intensive treatment group, the incidence of intravascular device and blood stream infections was 10-fold higher and the incidence of surgical site infections was 7-fold higher in the standard regimen group. The investigators recommended a target blood glucose concentration of <130 mg/dL for ICU patients.

### Conclusion

Hyperglycemia in hospitalized patients with and without diabetes increases morbidity, mortality, and costs. Correction of hyperglycemia in these patients reduces mortality, the risk of infections, and other adverse outcomes.

### References

- Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2005*. Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2005. [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2005.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf) (accessed 2006 Dec 19).
- Pan XR, Li GW, Hu YH et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997; 20:537-44.
- Hogan P, Dall T, Nikolov P, American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 2003; 26:917-32.
- Burke JP, Williams K, Gaskill SP et al. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from

- the San Antonio Heart Study. *Arch Intern Med* 1999; 159:1450-6.
- Koro CE, Bowlin SJ, Bourgeois N et al. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes. *Diabetes Care* 2004; 27:17-20.
- American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care* 2006; 29(suppl 1):S4-42.
- Clement S, Braithwaite SS, Magee MF et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; 27:553-91.
- Levetan CS, Passaro M, Jablonski K et al. Unrecognized diabetes among hospitalized patients. *Diabetes Care*. 1998; 21:246-9.
- Umpierrez GE, Isaacs SD, Bazargan N et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87:978-82.
- ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association. Consensus statement on inpatient diabetes and glycemic control: a call to action. *Diabetes Care*. 2003; 29:1955-62.
- Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA*. 2001; 286:1945-8.
- Rosmarin DK, Wardlaw GM, Mirtallo J. Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract*. 1996; 11:151-6.
- Watters JM, Kirkpatrick SM, Hopbach D et al. Aging exaggerates the blood glucose response to total parenteral nutrition. *Can J Surg* 1996; 39:481-5.
- Hollingsdal M, Juhl CB, Dall R et al. Glucocorticoid induced insulin resistance impairs basal but not glucose entrained high-frequency insulin pulsatility in humans. *Diabetologia* 2002; 45:49-55.
- Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med* 2003; 355:1903-11.
- Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA*. 2002; 288:2579-88.
- Bhisitkul RB. Vascular endothelial growth factor biology: clinical implications for ocular treatments. *Br J Ophthalmol*. 2006; 90:1542-7.
- The PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: initial results of the Protein Kinase C beta Inhibitor Diabetic Retinopathy Study (PKC-DRS) multicenter randomized clinical trial. *Diabetes* 2005; 54:2188-97.
- American Diabetes Association. Gestational diabetes mellitus. Position statement. *Diabetes Care* 2004; 27(suppl 1):S88-90.
- Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003; 78:1471-8.

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21. Pomposelli JJ, Baxter JK 3rd, Babineau TJ et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr*. 1998; 22:77-81.
22. Capes SE, Hunt D, Malmberg K et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000; 355:773-8
23. Estrada CA, Young JA, Nifong LW et al. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg* 2003; 75:1392-9
24. Williams LS, Rotich J, Qi R et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 2002; 59:67-71.
25. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract*. 2004; 10(suppl 2):21-33
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. Malmberg K, for the 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; 314:1512-5
28. Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med* 2001; 345:1359-67.
29. 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; 31:359-66
30. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; 79:992-1000
31. Bloomgarden ZT. Inpatient diabetes control: rationale. *Diabetes Care* 2004; 27:2074-80.

# Hyperglycemia management in the hospital setting

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Until recently, the management of hyperglycemia in hospitalized patients was not a top priority for clinicians, especially if the patient had no history of diabetes. However, hyperglycemia is associated with considerable morbidity and mortality in hospitalized patients with and without diabetes, and efforts to prevent and treat hyperglycemia have been shown to reduce morbidity, mortality, and costs (see the preceding article by Campbell in this supplement).<sup>1</sup> Therefore, the management of hyperglycemia has taken a higher priority in recent times. Achieving and maintaining glycemic control should be part of the therapeutic plan in hospitalized patients, regardless of whether the patient has a history of diabetes.

## Therapeutic Goals

The target blood glucose concentration range and treatment regimen needed to provide optimal glycemic control vary from one area of the hospital to another and from one type of patient to another. Recently, recommendations have been made for the target blood glucose concentration ranges in different hospital settings and types of patients based on randomized trials and obser-

**Purpose.** Recommendations for target blood glucose concentrations; factors that can complicate glycemic control; considerations that determine the aggressiveness of therapy to manage blood glucose levels; the role of oral antihyperglycemic drug therapy, sliding-scale insulin, continuous intravenous (i.v.) insulin infusions, and basal-bolus insulin therapy; the pharmacodynamics of various insulin products; computer decision support systems; and discharge planning for hospitalized patients with hyperglycemia are described.

**Summary.** Target blood glucose concentrations depend on whether patients are critically ill or not. Factors that can complicate glycemic control include the severity of illness, medications, and inconsistent dietary intake. The expected course of treatment, anticipated length of stay, and preadmission glycemic control influence the aggressiveness of therapy to manage hyperglycemia. The usefulness of oral antihyperglycemic agents for managing in-hospital hyperglycemia is limited by difficulty titrating the dosage and promptly achieving target blood glucose concentrations. Sliding-scale insulin is not recommended because it is ineffective and potentially dangerous. Continuous i.v. insulin therapy or intermittent subcutaneous (s.c.) basal-bolus plus correction injections

is preferred. Basal-bolus plus correction insulin therapy usually involves a single daily dose of insulin glargine at bedtime to prevent gluconeogenesis and ketogenesis, bolus injections of a rapid-acting insulin shortly before or after meals to meet prandial requirements, and correction bolus injections of rapid-acting insulin as needed for blood glucose elevations before or between meals. Hypoglycemia is the primary limiting factor for achieving optimal glycemic control with insulin therapy. Computer decision support systems can help reduce the risk of insulin infusion rate calculation errors and standardize insulin therapy. Communication with the primary care physician in the outpatient setting is an important part of discharge planning.

**Conclusion.** Sliding-scale insulin is not effective. Continuous i.v. insulin therapy or intermittent s.c. basal-bolus plus correction injections is preferred. Proactive management of hyperglycemia using these methods is needed to achieve and maintain glycemic control in hospitalized patients.

**Index terms:** Antidiabetic agents; Computers; Decision-making; Dosage schedules; Errors, medication; Hospitals; Hyperglycemia; Insulin; Insulin glargine; Insulins; Nutrition; Pharmacodynamics; Toxicity

**Am J Health-Syst Pharm.** 2007; 64:59-14

ational studies (Table 1).<sup>2,4</sup> These recommendations are based on a limited number of studies, primarily

in intensive care units (ICUs). The results of these studies have been extrapolated for non-ICU patients.

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Based on the proceedings of a symposium held December 4 and 6, 2006, during the ASHP Midyear Clinical Meeting, Anaheim, CA, and supported by an educational grant from Eli Lilly and Company. Dr. Hassan received an honorarium for his participation in the sym-

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DOI 10.2146/ajhp070102

Table 1.  
**Recommendations for Target Blood Glucose Concentrations<sup>2-4,a</sup>**

Patient Setting or Type of Patient	Source of Recommendations		
	American Diabetes Association	American College of Endocrinology/ American Association of Clinical Endocrinologists	Bode et al.
ICU or critically ill	As close to 110 mg/dL as possible and <180 mg/dL	<110 mg/dL	80-110 mg/dL
Non-ICU or non-critically ill	Preprandial: 90-130 mg/dL	Preprandial: <110 mg/dL	90-140 mg/dL
	Postprandial: <180 mg/dL	Postprandial: <180 mg/dL	
Pregnant	No recommendations found	Preprandial and during labor and delivery: <100 mg/dL 1-hour postprandial: <120 mg/dL	70-100 mg/dL

<sup>a</sup>ICU = intensive care unit.

### Glucose management

Various factors (Table 2) can cause hyperglycemia and complicate glycemic control in hospitalized patients (see the preceding article in this supplement by Campbell). Heart failure, renal and liver disease, malignancy, infection, and sepsis can lead to hyperglycemia or hypoglycemia in patients with and without diabetes.<sup>1</sup> Interruptions in meal and medication schedules can cause or worsen hyperglycemia, and these interruptions are common in a hospital setting where care provided by different departments (e.g., dietary, nursing pharmacy) often is not coordinated.

Several factors should be considered when determining the aggressiveness of inpatient therapy to manage blood glucose concentrations. These factors include the expected course of treatment, anticipated length of stay, and quality of preadmission glycemic control. The length of stay often depends on the hospital setting (e.g., ICU, surgical ward).

Oral antihyperglycemic agents sometimes are used in the hospital

setting for non-critically ill patients who received such therapy as outpatients, were admitted with good glycemic control, and are expected to eat normally during their hospitalization.<sup>6</sup> However, no large, well-designed clinical studies have been conducted to demonstrate a favorable impact on outcomes from oral antihyperglycemic drug therapy in hospitalized patients. The usefulness of oral antihyperglycemic agents for managing in-hospital hyperglycemia is limited by difficulty titrating the dosage and promptly achieving normal or near-normal blood glucose concentrations. Sulfonylureas have a long duration of action, and there is a risk of hypoglycemia in patients with limited food intake.<sup>1</sup> Metformin is contraindicated in many critically ill patients (e.g., patients with renal failure or congestive heart failure) because of an increased risk of lactic acidosis. Thiazolidinediones increase intravascular volume, which is a problem for patients predisposed to congestive heart failure or altered hemodynamics (e.g., myocardial ischemia).<sup>1</sup>

Insulin is the most clinically effective and cost-effective therapy for managing hyperglycemia in the hospital setting. Endogenous insulin requirements usually increase during critical illness, and exogenous insulin therapy can be readily adapted to meet acute needs.<sup>1</sup> Basal insulin administration prevents gluconeogenesis and ketogenesis. Insulin therapy can be individualized to meet a patient's nutritional needs, which depend on whether he or she is receiving intravenous (i.v.) dextrose, parenteral nutrition, enteral feedings, or meals.<sup>1</sup>

Most hospitalized patients require insulin therapy, especially if their blood glucose concentration is elevated at the time of admission or glycemic control deteriorates during their hospital stay.<sup>7</sup> In the ICU setting insulin usually is administered as a continuous i.v. infusion using regular insulin. Several validated insulin treatment protocols and treatment algorithms have been developed.<sup>8-10</sup> Some of these protocols and algorithms are not used because they attempt to accommodate the enormous number of possible clinical scenarios and are not user friendly. Computerized decision support software systems are advancing the use of computer technology in diagnostic and therapeutic decisions.<sup>11</sup> The most useful insulin treatment protocols facilitate dosage adjustments based on the rate of change of blood glucose concentration. Frequent blood glucose monitoring (i.e., hourly in the ICU) is needed to ensure that insulin therapy is appropriate and to prevent hypoglycemia. As the patient's condition and glycemic control improve and preparations are made to discharge the patient from the ICU, a transition from i.v. to subcutaneous (s.c.) insulin therapy may be made.

### Sliding-scale insulin

Sliding-scale insulin (i.e., i.v. or s.c. administration of a pre-established amount of regular insulin in response

to hyperglycemia) has traditionally been used in the hospital setting. However, sliding-scale insulin generally is inappropriate because it is a reactive approach to managing blood glucose concentrations that does not take into consideration previous insulin administration, the timing of food intake, or a patient's insulin sensitivity.<sup>1,3,6</sup> The use of sliding-scale insulin is ineffective and potentially dangerous as it can lead to rapid changes in blood glucose concentration and hypoglycemia or hyperglycemia.<sup>1</sup> In many cases, orders written for sliding-scale insulin at the time of hospital admission are never adjusted over the course of the hospital stay.<sup>12</sup> Sliding-scale insulin has also been reported to lengthen the duration of stay.<sup>13</sup>

### Basal-bolus insulin therapy

Proactive strategies should be developed to manage blood glucose

concentrations by mimicking normal physiologic patterns of endogenous insulin secretion using a combination of human insulins and insulin analogues (Table 3). In making the transition from continuous i.v. insulin therapy to intermittent s.c. injections, the i.v. insulin dosage should be divided into scheduled basal and prandial (i.e., meal-related) components. An intermediate- or long-acting insulin (often a single daily dose of insulin glargine at bedtime) should be used for basal insulin requirements and a short- or rapid-acting insulin should be used as a bolus injection before meals for prandial insulin requirements.<sup>19</sup> Basal insulin administration prevents gluconeogenesis and ketogenesis.<sup>1</sup> Prandial insulin doses usually are given before meals to promote glucose uptake by muscle tissue. In practice, it often is difficult to use regular insulin for prandial doses because of the need to administer it at least 30 minutes before meals, which is difficult to arrange in a hospital setting.<sup>1</sup>

Long or intermediate acting insulins are preferred for basal insulin administration. NPH and glargine are the agents typically used. Supplemental correctional doses using a rapid- or short-acting insulin (usually the same type of insulin as that used for prandial doses, lispro or aspart, for the sake of simplicity and to prevent error) may be used if blood glucose levels are elevated before or between meals or hyperglycemia occurs in a patient who is not eating.<sup>1</sup>

Correctional supplemental doses are anticipatory whereas sliding-scale doses are not.

The use of NPH insulin does not mimic normal endogenous basal insulin secretion. The duration of action of NPH insulin often falls short of 24 hours.<sup>16</sup> Peaks in glucose-lowering activity are pronounced and absorption is variable, leading to unpredictable hypoglycemia, which limits dosage adjustments.<sup>20</sup>

Insulin glargine offers many advantages over NPH insulin for meeting basal needs.<sup>20</sup> Insulin glargine has a longer duration of action (up to 24 hours), and no pronounced peak in activity.<sup>16,20</sup> The absorption characteristics of insulin glargine are consistent regardless of the administration site.<sup>21</sup> The risk of hypoglycemia and weight gain is lower with insulin glargine than with NPH insulin.<sup>20</sup> The 24-hour duration of action allows once daily administration. Insulin glargine is available as a clear liquid, not a suspension, so gentle agitation prior to administration is not necessary.<sup>21</sup> However, there is a potential for confusing it with rapid- and short-acting insulins, which also are clear liquids. Insulin glargine may not be mixed with other insulins.<sup>21</sup>

Insulin detemir is a new long-acting insulin that lacks pronounced peaks in activity.<sup>22</sup> Insulin detemir appears to provide better glycemic control with a lower risk of hypoglycemia and weight gain than NPH insulin and insulin glargine.<sup>23</sup> In one study of patients with type 1 diabe-

Table 2.  
**Factors Complicating Glucose Management<sup>1,5</sup>**

- Severity of illness
- Medications (e.g., glucocorticoids)
- Inconsistent dietary intake
- Patient nutritional status
- Prevailing blood glucose concentration
- History and type of diabetes and pre-hospital diabetes treatment regimen

Table 3.  
**Pharmacodynamics of Human Insulins and Insulin Analogues<sup>14-18,a</sup>**

Type of Insulin	Insulin Product	Time to Onset of Action (hr)	Time to Peak Effect (hr)	Duration of Action (hr)
Rapid acting	Insulin lispro, aspart, and glulisine	≤0.5	0.5–3	3–6
Short-acting	Regular human insulin	0.5–1	1–5	6–10
Intermediate-acting	NPH human insulin	1–2	4–14	10–24
Long-acting	Insulin glargine and detemir	1–2	Not applicable (has no peak)	~24 for glargine 6–23 for detemir

<sup>a</sup>The pharmacodynamics of any insulin product may vary among different individuals or at different times in the same individual.

tes, less intra-subject variability in glucose-lowering activity was found with insulin detemir than with insulin glargine or NPH insulin.<sup>24</sup> However, few comparative studies of insulin detemir and insulin glargine have been performed, so the role of insulin detemir in basal therapy remains to be clarified. Insulin detemir is a clear solution that usually is administered once daily with the evening meal or at bedtime or twice daily in the morning and at bedtime.<sup>22</sup>

Rapid-acting insulins are administered immediately before meals (or within 20 min after starting a meal for insulin glulisine).<sup>17</sup> Dosing should be conservative for patients whose dietary intake is uncertain.

In most diabetic patients with well-controlled blood glucose levels, the ratio of the total daily basal insulin dosage to the daily prandial insulin dosage is roughly 1:1.<sup>1</sup> The dosage adjustments for insulin glargine and insulin detemir usually are based on the morning fasting blood glucose concentration, and dosage adjustments for NPH insulin are based on fasting blood glucose values measured in the morning or before the evening meal.<sup>7</sup> If correction doses are consistently required, the basal insulin dose should be increased by roughly 50% of the total amount given as correction doses the preceding day.

Prandial dose adjustments are based on blood glucose concentrations measured before the midday meal and at bedtime. These adjustments are designed to prevent postprandial hyperglycemia and hypoglycemia.

Insulin dosing requirements are increased by illness and decreased when dietary intake is diminished.<sup>1</sup> Patients who are not taking anything by mouth often receive regular insulin by continuous i.v. infusion, with correction doses of short- or rapid-acting insulin. Prandial doses are not required because of the absence of dietary intake.

In patients who are eating meals and received s.c. insulin therapy before hospitalization with good glycemic control, the pre-hospitalization insulin regimen may be used with a modest dosage reduction to account for what typically is a lower dietary intake during the hospital stay. However, an increase in dosage may be needed if glycemic control was poor in the outpatient setting. Switching from s.c. therapy to continuous i.v. insulin infusion may be required if glycemic control deteriorates in these patients.

Patients receiving continuous enteral tube feedings (but not meals) receive basal insulin therapy plus correction doses (e.g., regular insulin every six hours). No prandial doses are required because nutrients are delivered continuously instead of at discrete mealtimes. Intravenous dextrose should be administered if enteral tube feedings are interrupted.

Patients receiving parenteral nutrition receive regular insulin in the parenteral nutrient solution to meet basal needs.<sup>1</sup> Regular insulin also may be used for correction doses.

The approach to managing hyperglycemia often hinges on the blood glucose concentration measured at the time of hospital admission. If it is 200 mg/dL or higher, basal-bolus s.c. insulin therapy usually is appropriate.<sup>7</sup> However, if the concentration is 300-400 mg/dL or higher or control is not promptly achieved with s.c. therapy, continuous i.v. insulin infusion is indicated.<sup>7</sup>

Switching from continuous i.v. insulin therapy to s.c. therapy is a complex matter that requires evaluation of the patient's condition and recent insulin dosage requirements. The total daily insulin requirement is extrapolated from the average infusion rate measured during a stable 4- to 8-hour period of continuous infusion.<sup>4</sup> Approximately 50-80% of the total daily insulin requirement is given as s.c. basal insulin in patients who are not eating meals.<sup>4</sup> If and

when dietary intake is resumed, this basal insulin is continued and prandial s.c. boluses are added based on the carbohydrate intake. If the blood glucose concentration remains above the target therapeutic range, correction doses of rapid-acting insulin are given before meals, at bedtime, and at 3am in addition to continuing basal-bolus therapy.<sup>4</sup>

### Preventing hypoglycemia

Hypoglycemia is the primary limiting factor for achieving optimal glycemic control with insulin therapy. Insulin dosage reductions may be required to prevent hypoglycemia if oral food intake, enteral feeding, parenteral nutrition, or i.v. dextrose is discontinued or decreased; meals are delayed because of a medical procedure; or the dosage of a glucocorticoid is reduced.<sup>1</sup> Blood glucose should be closely monitored if any of these events occurs.

The possibility of an inaccurate blood glucose measurement should be considered before making insulin dosage adjustments in the hospital setting. Blood glucose determinations are made using finger sticks before meals and at bedtime. Early postprandial measurements (i.e., within two to three hours after a meal) may lead to hypoglycemia and should be avoided, except in special circumstances, such as pregnant women.<sup>7</sup>

### Computer decision support systems

Ideally, continuous i.v. insulin therapy would be frequently and automatically adjusted based on blood glucose measurements taken hourly. A closed-loop computer system that would be completely automated, without the need for input from a clinician, could facilitate delivery of such therapy. An open-loop computer-assisted system that calculates infusion rates based on blood glucose data entered by a clinician has been developed and tested in humans in

various hospital settings.<sup>25</sup> This decision support system is based on a computer software program called Glucommander that was developed from a linear regression model and basal insulin requirement data for a large number of patients. The appropriate insulin infusion rate for an individual is calculated by the computer software based on the observed rate of change of blood glucose concentrations, and these calculations are repeated frequently to provide continuous variable rate i.v. insulin therapy.

Based on the linear regression analysis, a starting infusion rate in units/hour was calculated by subtracting 60 mg/dL from the patient's measured blood glucose concentration and multiplying the result by 0.02.<sup>25</sup> The blood glucose level was monitored hourly, and the multiplier was adjusted to keep the blood glucose concentration in the target range. For example, if the blood glucose concentration exceeded 140 mg/dL and had not decreased by 15% during the preceding hour in a non-ICU patient, the multiplier was increased by 0.01. If the blood glucose concentration fell below 100 mg/dL, the multiplier was decreased by 0.01. No change was made to the multiplier if the blood glucose concentration was in the target range (100-140 mg/dL). If the blood glucose fell below 80 mg/dL, the blood glucose concentration was subtracted from 100 mg/dL, and the result was multiplied by 0.4 to determine the number of milliliters of 50% dextrose in water to administer. If the patient resumed oral dietary intake, the infusion was continued until two hours after the initiation of s.c. insulin therapy and then discontinued.

The computer decision support system was effective for correcting hyperglycemia within three hours, with a low risk of hypoglycemia.<sup>25</sup> Such systems hold promise for reducing the risk of insulin infusion

rate calculation errors, which is a major safety concern in efforts to provide continuous variable rate i.v. insulin therapy, and standardizing insulin therapy.

#### Discharge planning

Blood glucose levels should be stabilized and the treatment regimen for the management of hyperglycemia should be simplified to the extent possible before patient discharge from the hospital. Follow-up care should be provided within several weeks after discharge. Blood glucose levels should be monitored after discharge in patients with pre-diabetes or in-hospital hyperglycemia that resolves prior to discharge as well as in patients with diabetes.<sup>26</sup> Communication with the primary care physician in the outpatient setting is an important part of discharge planning because this physician will need to provide follow-up care.

In patients with diabetes, the A1C should be measured before discharge if it was not measured within the preceding several months. Changes in diet, exercise, and physiological stress after discharge may affect blood glucose concentrations and medication requirements, so self-monitoring of blood glucose and follow-up care are needed.

The hospital setting provides an excellent opportunity for patients with newly diagnosed diabetes to receive education about the disease and the patient's role in self-care. The patient should be referred to a diabetes educator and provided with specific instructions for proper medication use (especially insulin dose preparation and self-administration techniques), self-monitoring of blood glucose, and hypoglycemia and hyperglycemia prevention and recognition. Patients should be educated about the target blood glucose concentrations and the signs and symptoms suggesting a need to contact their healthcare provider.

#### Future research

Although much has been learned about the harmful effects of hyperglycemia and the benefits of hyperglycemia correction in hospitalized patients (see the preceding article by Campbell in this supplement), several unresolved questions remain to be addressed in future research. The contribution of tight blood glucose control to outcomes in hospitalized patients, the precise target for blood glucose concentrations, the appropriateness of extrapolating target blood glucose data from ICU patients to non-ICU patients, and the types of patients who are most likely to benefit from aggressive treatment of hyperglycemia are unclear at this time. The optimal mode of insulin administration also remains to be determined.

#### Conclusion

Proactive management of hyperglycemia is needed to achieve and maintain glycemic control in hospitalized patients. Administering insulin by continuous i.v. infusion or intermittent basal-bolus plus correction-dose s.c. injections is safe and effective for meeting these goals.

#### References

1. Clement S, Braithwaite SS, Magee MF et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; 27:553-91.
2. American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care* 2006; 29(suppl 1):S4-42.
3. 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. [www.aace.com/pub/pdf/guidelines/InpatientDiabetesPositionStatement.pdf](http://www.aace.com/pub/pdf/guidelines/InpatientDiabetesPositionStatement.pdf) (accessed 2006 Dec 20).
4. Bode BW, Braithwaite SS, Steed RD et al. Intravenous insulin infusion therapy: indications, methods, and transition to subcutaneous insulin therapy. *Endocr Pract.* 2004; 10(suppl 2):71-80.
5. Luna B, Feinglos MN. Drug-induced hyperglycemia. *JAMA.* 2001; 286:1945-8.
6. ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabe-

- tes and glycemic control: a call to action. *Diabetes Care* 2006; 29:1955-62.
7. Inzucchi, SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med*. 2006; 355:1903-11.
  8. Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med* 2001; 345:1359-67.
  9. 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.
  10. 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.
  11. Garg AX, Adhikari NK, McDonald H et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes. *JAMA*. 2005; 293:1223-38.
  12. 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.
  13. Browning LA, Dumo P. Sliding-scale insulin: an antiquated approach to glycemic control in hospitalized patients. *Am J Health-Syst Pharm* 2004; 61:1611-4.
  14. Mudaliar S, Edelman SV. Insulin therapy in type 2 diabetes. *Endocrinol Metab Clin North Am* 2001; 30:935-82.
  15. McEvoy GK, ed. Insulins general statement. In: AHFS Drug Information 2006 Bethesda, MD: American Society of Health-System Pharmacists; 2006:3086-95.
  16. Lepore M, Pampanelli S, Fanelli C et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; 49:2142-8.
  17. Apidra package insert. Kansas City, MO: Aventis Pharmaceuticals Inc.; November 2005.
  18. Plank J, Bodenlenz M, Simmer F et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care* 2005; 28:1107-12.
  19. Leahy JL. Intensive insulin therapy in type 1 diabetes mellitus. In: Leahy JL, Cefalu WW, eds. *Insulin Therapy*. New York, NY: Marcel Dekker Inc.; 2002:87-112.
  20. Campbell RK, White JR, Levien T et al. Insulin glargine. *Clin Ther*. 2001; 23:1938-57.
  21. McEvoy GK, ed. Insulin glargine. In: AHFS Drug Information 2006 Bethesda, MD: American Society of Health-System Pharmacists; 2006:3098-9.
  22. Levemir package insert. Princeton, NJ: Novo Nordisk Inc.; October 2005.
  23. Peterson GE. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. *Curr Med Res Opin*. 2003; 22:2613-9.
  24. Heise T, Nosek L, Ronn BB et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 2004; 53:1614-20.
  25. Davidson PC, Steed RD, Bode BW. Glucomander: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120/618h of operation. *Diabetes Care* 2005; 28:2418-23.
  26. Levetan CS, Passaro M, Jablonski K et al. Unrecognized diabetes among hospitalized patients. *Diabetes Care* 1998; 21:246-9.

# Hospital protocols for targeted glycemic control: Development, implementation, and models for cost justification

MICHELLE F. MAGEE

Efforts to develop best practices for enabling targeted glycemic control in the hospital setting require consideration of multiple factors.<sup>1</sup> Identification and documentation of all patients with hyperglycemia regardless of whether they have a known diagnosis of diabetes is key. Comorbid conditions, diabetes complications, and the level of blood glucose control should be documented. The initial patient assessment, physical examination, laboratory testing and an individualized management plan for optimal blood glucose control will also be incorporated.

Best practices will specify upper limits for blood glucose concentration for non-pregnant adults in both intensive care units (guidelines suggest 110 mg/dL) and non-critical care areas of the hospital (usually 110 mg/dL to 180 mg/dL).<sup>1,2</sup> The minimum frequency of finger stick blood glucose monitoring also will be designated. Monitoring parameters should include A1C measured at the time of admission unless it was measured within the preceding

**Purpose.** Evolving elements of best practices for providing targeted glycemic control in the hospital setting, clinical performance measurement, basal-bolus plus correction-dose insulin regimens, components of standardized subcutaneous (s.c.) insulin order sets, and strategies for implementation and cost justification of glycemic control initiatives are discussed.

**Summary.** Best practices for targeted glycemic control should address accurate documentation of hyperglycemia, initial patient assessment, management plan, target blood glucose range, blood glucose monitoring frequency, maintenance of glycemic control, criteria for glucose management consultations, and standardized insulin order sets and protocols. Establishing clinical performance measures, including desirable processes and outcomes, can help ensure the success of targeted hospital glycemic control initiatives. The basal-bolus plus correction-dose regimen for insulin administration will be used to mimic the normal physiologic pattern of endogenous insulin secretion. Standardized insulin order sets and protocols are being used to minimize the risk of error in insulin therapy. Components of standardized s.c. insulin order sets include specification of the hyperglycemia diagnosis, finger stick

blood glucose monitoring frequency and timing, target blood glucose concentration range, cutoff values for excessively high or low blood glucose concentrations that warrant alerting the physician, basal and prandial or nutritional (i.e., bolus) insulin, correction doses, hypoglycemia treatment, and perioperative or procedural dosage adjustments. The endorsement of hospital administrators and key physician and nursing leaders is needed for glycemic control initiatives. Initiatives may be cost justified on the basis of the billings for clinical diabetes management services and/or the return-on-investment accrued to reductions in hospital length of stay, readmissions, and accurate documentation and coding of unrecognized or uncontrolled diabetes, and diabetes complications.

**Conclusion.** Standardized insulin order sets and protocols may minimize risk of insulin errors. The endorsement of these protocols by administrators, physicians, nurses, and pharmacists is also needed for success.

**Index terms:** Blood levels; Costs; Dextrose; Diagnosis; Disease management; Dosage; Economics; Errors, medication; Hospitals; Hyperglycemia; Insulin; Insulins; Methodology; Models; Protocols

**Am J Health-Syst Pharm.** 2007; 64:S15-20

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Based on the proceedings of a symposium held December 4 and 6 2006 during the ASHP Midyear Clinical Meeting, Anaheim, CA, and supported by an educational grant from Eli Lilly and Company.

Dr. Magee received an honorarium for her participation in the symposium and for the preparation of this article. Dr. Magee reports that she has research and education grant support from and speaks for sanofi-aventis, NovoNordisk, and Eli Lilly and Company.

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DOI 10.2146/ajhp070103

month, and the result is documented in the medical record. The A1C is used increasingly in the inpatient setting although historically it has been thought of as an outpatient monitoring tool. In patients with no known history of diabetes, the A1C can help differentiate between diabetes, prediabetes, and stress- or illness-related hyperglycemia, although other tests are needed for diagnostic purposes. In patients with diabetes, the admission A1C provides insight about the adequacy of the outpatient antidiabetes regimen, allowing an opportunity to adjust therapy if preadmission control was suboptimal.

Monitoring and documentation of finger stick blood glucose testing at least four times daily is recommended. Daily review of blood glucose values is crucial and must be assessed in the context of exogenous insulin dosage requirements, and adjustment of the treatment regimen at least once daily to enable targeted blood glucose control. Guidance should be provided to the nursing staff about what constitutes an excessively high or low blood glucose concentration (e.g., >400 mg/dL, <40 mg/dL), which will warrant alerting the physician.<sup>1</sup>

Criteria for considering a consultation with an endocrinologist or diabetes expert might include persistent hyperglycemia; severe or recurrent hypoglycemia (e.g., two or more episodes within a 24-hour period despite intervention); major surgery; diabetic ketoacidosis (DKA); hyperosmolar hyperglycemic state; acute macrovascular event, serious infection, and a non-healing wound.<sup>1</sup>

Standardized order sets and protocols to guide prescribers in ordering safe and effective insulin therapy are increasingly part of best practices for targeted glycemic control in the hospital. These protocols will typically address the management of hypoglycemia; insulin administration by continuous intravenous (i.v.) infusion; the transition from

continuous i.v. therapy to intermittent subcutaneous (s.c.) injections; s.c. insulin orders; and perioperative insulin orders.<sup>1</sup> The development of insulin order sets for other special circumstances (e.g., the use of external insulin pumps, patients receiving high-dose glucocorticoid therapy or enteral or parenteral nutrition) is increasingly common.

### Clinical performance measurement

Establishing measures for clinical performance is vital to the successful implementation of a targeted glycemic control initiative. Clinicians must be made aware of these clinical performance measures and methods that will be applied to assist with their implementation.

A set of clinical performance measures, which have been put forward by the University HealthSystem Consortium (UHC), a group of university hospitals throughout the U.S., is shown in Table 1.<sup>3</sup> Some measures reflect desired processes and outcomes (e.g., maximum blood glucose values the morning of hospital day two, which reflect prompt and effective management of hyperglycemia).

Other measures (e.g., the number of patients receiving antihyperglycemic medication with a blood glucose >200 mg/dL) suggest opportunities for improved patient care. Basal insulin therapy may be used as an indicator of the appropriateness of insulin therapy. Basal insulin data can generally be obtained from pharmacy databases. Requirements for frequent measurement of blood glucose and compilation of blood glucose values facilitate glucometrics, the systematic analysis of blood glucose results. The UHC recommendation for an i.v. insulin protocol for the surgical ICU is typically extended to include all ICUs in the hospital.

### Insulin therapy

Insulin is the preferred therapy for hyperglycemia in hospital inpatients because it can be more rapidly titrated to meet the changing glycemic requirements of acute illness than oral antihyperglycemic therapy.<sup>3</sup> The use of standardized insulin order sets and protocols is among several strategies that is being used to enable targeted blood glucose control and to minimize the risk of errors associated with insulin therapy in hospitalized patients.

Table 1. University HealthSystem Consortium Clinical Performance Measures for Glycemic Control<sup>3,a</sup>

- Diagnosis of diabetes mellitus documented in patient medical record
- A1C documented in patient medical record
- Blood glucose measured within 8 hr after admission
- Finger stick blood glucose measured at least four times daily
- ICU blood glucose measured on the morning of hospitalization day 2 ≤110 mg/dL
- Non-ICU blood glucose measured on the morning of hospitalization day 2 ≤180 mg/dL
- Number of patients with blood glucose >200 mg/dL on all hospitalization days receiving antihyperglycemic medication
- Number of patient days with blood glucose <50 mg/dL
- Appropriate insulin therapy given
- All point-of-care blood glucose values and insulin doses for a patient listed together on one flow sheet
- Hypoglycemia protocol established
- Appropriate handling of hypoglycemic episodes
- Mandatory i.v. insulin protocol established for SICU

<sup>a</sup>ICU = intensive care unit; i.v. = intravenous; SICU = surgical intensive care unit.

Other strategies include computerized physician order entry and inclusion in the formulary of insulin pens, which may help prevent dose measurement errors that can be associated with the use of vials and syringes.

The ideal insulin therapy protocol is user-friendly, effective for reaching glycemic goals, and safe, with minimal risk of hypoglycemia or other adverse effects. These protocols should include specific guidelines for treating hypoglycemia.

Protocols for the safe and effective administration of insulin i.v. infusion therapy in ICUs are well established in most hospitals.<sup>4</sup> Recent efforts have focused on the development of protocols for s.c. insulin therapy outside ICUs.

Most hospitalized patients with hyperglycemia receive s.c. insulin therapy during their stay. The use of traditional sliding-scale insulin is not recommended because it is associated with increased incidence of both hypoglycemia and hyperglycemia.<sup>25-7</sup> The preferred method for prescribing s.c. insulin is the Basal-bolus plus Correction-dose regimen, a method that mimics normal physiologic patterns of endogenous insulin secretion and may be referred to as "B-b-C."<sup>36</sup> Basal insulin will be administered on a regular schedule to suppress hepatic glucose production and prevent ketogenesis. Bolus insulin is given shortly before or after meals or with other nutritional sources to prevent post-nutritional hyperglycemia and to promote glucose uptake by muscle. Correction doses are used to treat hyperglycemia that occurs before or between meals or in patients who are not eating. Insulin glargine once daily or insulin detemir once or twice daily usually is preferred for basal therapy. NPH insulin twice daily also may be used; however, caution should be taken to prevent hypoglycemia when the NPH insulin peaks, particularly if oral intake is curtailed. Rapid-acting insulins or regular insulin are used for bolus doses and correction doses.

The rapid-acting insulins are preferred because timing and amount of dietary intake are difficult to predict in hospitals, and their rapid time to onset of action allows dosing directly with nutrition intake. In addition, it is feasible to reduce the dose of a rapid-acting insulin if only part of a meal is consumed, which again helps avoid hypoglycemia. Regular insulin administration must take place 30-45 minutes before meals, and patients who fail to eat as much as anticipated or experience a delay in nutrition delivery may experience hypoglycemia.<sup>6</sup>

Continuous i.v. and s.c. insulin infusions of regular (or rapid-acting) insulin may be used to meet basal needs and nutritional needs associated with i.v. dextrose, parenteral nutrition, enteral feedings, and nutritional supplements as well as meals.<sup>6</sup> However, it is increasingly being recognized that the continuous insulin infusion is optimally used to meet only basal needs combined with a s.c. rapid-acting insulin at mealtimes or with tube feedings to avoid hypoglycemia when reduction in nutritional intake occurs (e.g., overnight). Premixed insulins (e.g., 70/30) containing a fixed ratio of doses of two insulins is not recommended in acutely ill hospitalized patients because these products do not allow for titration of each component to meet rapidly changing insulin needs. Such products may be useful toward the end of a hospital stay after dosage titration is complete, when plans are made for patient discharge, and the convenience in self-administration on an outpatient basis becomes a consideration.

#### Subcutaneous insulin order sets

The core components of standardized s.c. insulin order sets are listed in Table 2. The hyperglycemia diagnosis (i.e., diabetes, stress- or illness-related hyperglycemia), including the type of diabetes (e.g., type 1, type 2, gestational, or other), whether dia-

betes is controlled or uncontrolled, and whether diabetes complications are present (if diabetes is diagnosed), can be built into the insulin order set. This will increase accuracy of documentation and coding of diabetes-related diagnoses, which has implications for the hospital in terms of reimbursement rates for Medicare and Medicaid services and some other insurance payors. It is also extremely important to differentiate type 1 diabetes from other forms of diabetes and hyperglycemia because exogenous insulin therapy is always required and in these cases should never be discontinued in patients with absolute insulin deficiency as DKA will result. The presence of uncontrolled diabetes and diabetes complications should be documented in the s.c.

The target blood glucose concentration range and criteria for determining what constitutes an excessively high or low level, which warrants alerting the physician, should also be specified. These values should be individualized based on patient-specific considerations (e.g., a particularly high risk for hypoglycemia).

Orders for basal and prandial or nutritional (i.e., bolus) insulin should specify the time of day, type of insulin, and number of units of insulin to administer. A scaled algorithm is commonly integrated (Table 2) to allow specification of orders for correction insulin doses based on the patient's finger stick blood glucose concentration and to incorporate an allowance for insulin sensitivity. Insulin sensitivity is estimated based on daily insulin requirements or body weight (obesity is associated with insulin resistance). An adult receiving low insulin doses (up to 40 units/day) or with a body weight < 70 kg typically is less insulin resistant than an adult receiving medium doses (41-99 units/day) or weighing 70-100 kg. The patient receiving high doses of insulin, exceeding 100 units/day, or weighing more than 100 kg will

Table 2.

**Core Components of Standardized Subcutaneous Insulin Order Sets**

1. Specification of the hyperglycemia-related diagnosis (stress/illness-related diabetes, or hyperglycemia)
  - Type of diabetes (type 1, type 2, other) and whether controlled or uncontrolled
  - Presence of diabetes complications
2. Finger stick blood glucose monitoring frequency (before meals and bedtime or every 4–6 hours timed to coincide with nutrition or if receiving nothing by mouth)
3. Target blood glucose range (e.g., 80-140 mg/dL)
4. Thresholds for high or low blood glucose values that warrant alerting the physician (e.g., >400 mg/dL, <40 mg/dL)
5. Scheduled/programmed basal and prandial or nutritional (bolus) insulin order<sup>a</sup>

	Breakfast 0700-0900	Lunch 1200-1300	Dinner 1700-1900	Bedtime 2200-2300
Basal	Give ___ units <input type="checkbox"/> insulin glargine <input type="checkbox"/> insulin detemir <input type="checkbox"/> NPH insulin		Give ___ units <input type="checkbox"/> insulin glargine <input type="checkbox"/> insulin detemir <input type="checkbox"/> NPH insulin	Give ___ units <input type="checkbox"/> insulin glargine <input type="checkbox"/> insulin detemir <input type="checkbox"/> NPH insulin
Prandial/nutritional (bolus)	Give ___ units <input type="checkbox"/> insulin lispro <input type="checkbox"/> insulin aspart <input type="checkbox"/> insulin glulisine <input type="checkbox"/> regular insulin	Give ___ units <input type="checkbox"/> insulin lispro <input type="checkbox"/> insulin aspart <input type="checkbox"/> insulin glulisine <input type="checkbox"/> regular insulin	Give ___ units <input type="checkbox"/> insulin lispro <input type="checkbox"/> insulin aspart <input type="checkbox"/> insulin glulisine <input type="checkbox"/> regular insulin	

6. Correction insulin dose algorithm

Select type of insulin:

insulin lispro,  insulin aspart,  insulin glulisine, or  regular insulin

Measured Blood Glucose Concentration (mg/dL)	Low-Dose (<40 units/day) or Body Weight <70 kg	Medium-Dose (41-99 units/day) or Body Weight 70-100 kg	High-Dose (>100 units/day)	Other (individualized)
150–199	Give 1 unit	Give 1 unit	Give 2 units	Give ___ units
200–249	Give 2 units	Give 3 units	Give 4 units	Give ___ units
250–299	Give 3 units	Give 5 units	Give 7 units	Give ___ units
300–349	Give 4 units	Give 7 units	Give 10 units	Give ___ units
>349	Give 5 units	Give 8 units	Give 20 units	Give ___ units

7. Hypoglycemia treatment

8. ± Perioperative or procedural adjustment to the insulin dosage

<sup>a</sup>Limit insulin choices to those preferred per individual hospital formulary for inpatient therapy.

require even higher correction doses of insulin.<sup>8</sup>

Order sets for s.c. insulin will also include guidelines for the management of hypoglycemia. General guidelines for adjustments to s.c. insulin therapy for patients undergoing surgery or other procedures may be included. Examples of such recommendations include giving all insulin doses as ordered the night before the procedure and 1/2 or 2/3 of the usual morning NPH insulin dose or 80%

of the usual insulin glargine dose on the morning of the procedure. If the patient is not eating one will withhold all morning regular or rapid-acting insulin dose unless the blood glucose concentration exceeds 200 mg/dL (or another predetermined value). Hyperglycemia will be treated with a conservative dose of bolus insulin in order to avoid hypoglycemia. Bolus insulin will be resumed when nutritional intake is resumed. For patients with high glucose, rapid-acting

correction dose insulin will be given whenever the blood glucose is high.

**Strategies for implementation**

The success of glycemic control initiatives in hospitals hinges on obtaining the endorsement of hospital administrators and key physician and nursing leaders. The hospital pharmacist may play a pivotal role in this process. Convincing the hospital administration and physician and nursing leadership to implement

a glycemic control protocol can be a labor-intensive process. Data documenting the benefits of targeted glycemic control (see the article on Etiology and Effect on Outcomes of Hyperglycemia in Hospitalized Patients by Campbell in this supplement) should be presented to hospital administrators and key decision makers among the physician and nursing staff.<sup>10,12</sup> Best practices for providing targeted glycemic control, including standardized insulin order sets, should be developed, presented to, and accepted by the front-line staff who provide patient care on a daily basis as well as by managers and administrators. It is important to note that these initiatives are not likely to be successful if there is grass roots resistance among front-line caregivers.

In many cases, initiatives are successful only because of the efforts of a champion (often a pharmacist, endocrinologist, intensivist, hospitalist, internist, or nurse) who works tirelessly and has the support of a multidisciplinary team that represents all diabetes care stakeholders and has made a commitment to performance improvement. Intensive education of all staff involved with or affected by the initiative (e.g., physicians, nurses, pharmacists, coding staff) is needed. Collection and analysis of data are needed to identify opportunities for further improvement and demonstrate a return-on-investment in the initiative.

#### Role of the pharmacist

Pharmacists can play a vital role in initiatives to improve glycemic control in hospitals by serving as champions who will spearhead glycemic control initiatives and efforts to implement insulin treatment protocols and standardized insulin order sets. Many of these efforts include pharmacists, who serve on the pharmacy and therapeutics committee. Pharmacists also can serve as advocates for the safe and effective use of

insulin therapy in the institution by providing education about physiologic basal-bolus insulin therapy and developing medication error reduction campaigns that target insulin therapy.

#### Financial justification

Two types of strategies may be used to cost justify glycemic control initiatives. Self-supporting strategies for cost justification of glycemic control initiatives are based on amounts billed by physicians, nurse practitioners, physician assistants, and others where a return-on-investment can be demonstrated for the provision of clinical diabetes management services. Hospital-based strategies justify these initiatives on the basis of reductions in hospital length of stay, increased "through put" (i.e., beds vacated for use by other patients), reduction in readmissions, increased accuracy in coding of uncontrolled diabetes, and diabetes co-morbidities (e.g., infections) or complications, and identification of previously unrecognized diabetes.

Uncontrolled diabetes is a non-specific term indicating that the treatment regimen does not maintain blood glucose concentrations within an acceptable range. Uncontrolled diabetes may be defined as an admission blood glucose concentration or two or more values during a hospital stay that exceeds 180 mg/dL or 200 mg/dL. Lesser persistent hyperglycemia also might warrant a designation of uncontrolled diabetes, although it would apply only to patients with a diagnosis of diabetes. Data supporting these strategies are currently available in the ICU setting; data for non-ICU settings are emergent. Several examples of the application of such strategies for cost justification follow.

In a 17-year prospective, nonrandomized study of 4864 patients with diabetes who underwent an open-heart surgical procedure, continuous i.v. insulin therapy designed to

achieve predetermined target blood glucose levels reduced the risk of deep sternal wound infections by 66% in a highly cost-effective manner.<sup>13</sup>

#### Impact of glycemic control initiatives on outcomes

The impact of an inpatient diabetes management program was compared before and after program implementation in a 750-bed hospital where 23% of patient discharges (a proportion that is not atypical) had a diagnosis of diabetes.<sup>14</sup> The program was based on a 2004 American Diabetes Association technical review of the management of diabetes and hyperglycemia in the hospital.<sup>6</sup> Staff resources devoted to the program were generous and included a program director, assistant, diabetes clinical specialist, physician director who was an endocrinologist, and one nurse case manager for every two patient care units. The program was implemented in 10 medical and surgical patient care units, including a medical intensive care unit (ICU) and other non-ICU settings. Three order sets were implemented for i.v. insulin infusions, the transition from i.v. infusions to s.c. insulin therapy, and s.c. insulin therapy, with basal, bolus, and supplemental correction doses. Extensive education about proper use of the order sets was provided to nurses and physicians. Nurse case managers monitored order set use and provided advice as needed to prescribers when the blood glucose concentration exceeded the upper limit of the target range.

Implementation of the program significantly reduced the average blood glucose concentration by 46 mg/dL in the medical ICU and 26 mg/dL throughout patient care settings, with no significant increase in the incidence of severe hypoglycemia (defined as a blood glucose concentration < 40 mg/dL).<sup>14</sup> Basal insulin prescribing increased after program implementation, reflecting an improvement in the appropriate-

ness of insulin prescribing. A 34% decrease in the incidence of central venous line infections was observed. If an estimated incremental cost of \$3700 to treat one central venous line infection is assumed, the cost savings associated with the observed reduction in infections definitely exceeds the cost of insulin therapy. Program implementation also resulted in a significant 0.26-day reduction in the average hospital length of stay among 6876 patient discharges, which translates to 1778 days saved, which was extrapolated to an annual cost savings of \$2.2 million and a 467% return-on-investment for the hospital.

In another example where return on investment for billable clinical glycemia management services has been shown for implementation of an inpatient blood glucose control team, validated protocols for i.v. and s.c. insulin therapy were used in 276 patients and 922 patients, respectively, as part of a surgical management service at a university-based hospital.<sup>15</sup> The average blood glucose concentration improved from 169 mg/dL to 135 mg/dL with i.v. therapy in 276 patients. In 922 patients receiving s.c. therapy, the blood glucose target (80-150 mg/dL) was achieved in 59% of patients and the clinically acceptable range (80-180 mg/dL) was achieved in 74% of patients. There was no significant increase in hypoglycemia after implementation of the protocols for i.v. or s.c. therapy. The revenue generated through clinical

billings for diabetes management services by the nurse practitioners fully supported this surgical management service, which included two nurse practitioners, 0.25 of a full-time equivalent (FTE) endocrinologist, and part of an FTE for a program administrator to perform billing functions. Thus, this surgical management service was self-supporting. Reductions in infections is one such approach to cost justifying glycemic control initiatives.

### Conclusion

Standardized insulin order sets and protocols can be implemented to guide prescribers in ordering safe and effective insulin therapy and are increasingly part of recognized best practices for safe and effective targeted glycemic control in the hospital.

### References

1. American Healthways Inpatient management guidelines for people with diabetes. Nashville, TN: American Healthways, Inc; 2004 May. [www.healthways.com/articles/guidelines/inpatient\\_guidelines\\_2004.pdf](http://www.healthways.com/articles/guidelines/inpatient_guidelines_2004.pdf) (accessed 2006 Dec 22).
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. [www.aace.com/pub/pdf/guidelines/InpatientDiabetesPositionStatement.pdf](http://www.aace.com/pub/pdf/guidelines/InpatientDiabetesPositionStatement.pdf) (accessed 2006 Dec 20).
3. The University HealthSystem Consortium (UHC) benchmarking project: evaluation of hospital glycemic control at academic medical centers (AHC). *Diabetes.* 2003; 55(suppl 1):437.
4. Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med.* 2003; 355:1903-11.
5. 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.
6. ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association Consensus statement on inpatient diabetes and glycemic control: A call to action. *Diabetes Care.* 2003; 29:1575-82.
7. Clement S, Braithwaite SS, Magee MF et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care.* 2004; 27:553-91.
8. 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.
9. Hirsch IB, Braithwaite SS, Verderese CA et al. Monograph: practical management of inpatient hyperglycemia. Hilliard Publishing LLC, 2005.
10. Malmberg K, for the 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; 314:1512-5.
11. Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med.* 2001; 345:1359-67.
12. 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; 31:359-66.
13. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract.* 2004; 10(suppl 2):21-33.
14. Newton CA, Young S. Financial implications of glycemic control: results of an inpatient diabetes management program. *Endocr Pract.* 2003; 12(suppl 3):43-8.
15. DeSantis AJ, Schmeltz LR, Schmidt K et al. Inpatient management of hyperglycemia: the Northwestern experience. *Endocr Pract.* 2003; 12:491-504.

## Improving glycemic control in hospital patients with and without diabetes mellitus

Article 204-000-07-003-H01  
Qualifies for 1.5 hours (0.15 CEU) of continuing education credit

### Learning objectives

After studying these articles, the reader should be able to

1. Describe the prevalence of diabetes mellitus in the United States, and identify a possible cause of hyperglycemia in hospitalized patients and a mechanism for harm from hyperglycemia.
2. Name an outcome in hospitalized patients that is adversely affected by hyperglycemia, and a documented benefit of intensive therapy to correct hyperglycemia in hospitalized patients.
3. Recommend the target blood glucose concentration for a patient based on his or her severity of illness, and identify a factor that can complicate glycemic control and a consideration in the aggressiveness of therapy to manage blood glucose levels.
4. Explain the limitations of oral antihyperglycemic drug therapy and sliding-scale insulin therapy, compare and contrast the pharmacodynamics of various insulin products, and explain how these products are used in a basal-bolus plus correction-dose insulin regimen for a patient previously receiving continuous intravenous (i.v.) insulin therapy.

5. List an element of best practices for providing targeted glycemic control in the hospital setting, a clinical performance measure, and a component of a standardized subcutaneous (s.c.) insulin order set, and devise a strategy to implement and cost justify a glycemic control initiative.

### Self-assessment questions

For each question there is only one best answer:

1. Which of the following figures represent the estimated number of Americans with diabetes mellitus and the subset with undiagnosed diabetes?
  - a. 28 million, including 0.6 million people who are undiagnosed.
  - b. 62 million, including 0.6 million people who are undiagnosed.
  - c. 146 million, including 62 million people who are undiagnosed.
  - d. 208 million, including 62 million people who are undiagnosed.

2. Which of the following is the most likely cause of hyperglycemia in a hospitalized patient in an intensive care unit?
  - a. Blood glucose measurement error.
  - b. Misdiagnosis.
  - c. Illness-related stress.
  - d. Pregnancy.
3. The B-b-C regimen refers to:
  - a. Breakfast, bedtime, and correction doses.
  - b. Basal, breakfast, and correction doses.
  - c. Bedtime, bonus, and correction doses.
  - d. Basal, bolus, and correction doses.
4. Which of the following is associated with high sorbitol levels, cataracts, and nerve damage in patients with long-term hyperglycemia?
  - a. Advanced glycosylation end product formation.
  - b. Inhibition of protein kinase C- $\beta$ .
  - c. Increases in aldose reductase.
  - d. Inhibition of C-reactive protein.
5. Activation of vascular endothelial growth factor and proliferative diabetic retinopathy in patients with diabetes are attributed to:
  - a. Hyperglycemia-related activation of protein kinase C- $\beta$ .
  - b. Hyperglycemia-related immune system dysfunction.
  - c. Hyperglycemia-related deposition of advanced glycosylation end products.
  - d. Hyperglycemia-related metabolism of glucose to sorbitol by aldose reductase.

- 6 Which of the following outcomes has been demonstrated with intensive therapy to correct hyperglycemia in hospitalized patients?
- Increased incidence of infection and rejection in organ transplant recipients
  - Reduced progression of pre-diabetes to diabetes
  - Reduced risk of hypercholesterolemia and myocardial infarction.
  - Reduced risk of mortality and infection.
- 7 According to the American College of Endocrinology and American Association of Clinical Endocrinologists, which of the following should be the upper limit for blood glucose concentration in a critically ill patient in an intensive care unit?
- 100 mg/dL
  - 110 mg/dL
  - 130 mg/dL
  - 150 mg/dL
- 8 Which of the following target blood glucose concentrations was recommended to reduce the risk of nosocomial infection in patients in intensive care units based on a small prospective study comparing a standard insulin regimen with intensive insulin treatment?
- < 110 mg/dL
  - < 130 mg/dL
  - < 150 mg/dL
  - < 180 mg/dL
- 9 Oral antihyperglycemic drug therapy is not widely used for hospitalized patients with diabetes because of:
- The need to stock many different products, some of which are costly.
  - The inability of critically ill patients to take anything by mouth.
  - The lack of efficacy in reducing blood glucose concentrations on a long-term basis
  - The difficulty in promptly achieving target blood glucose concentrations
- 10 Sliding-scale insulin is not recommended for hospitalized patients with hyperglycemia because:
- It is labor-intensive to individualize doses based on previous blood glucose values
  - It is labor-intensive to take into consideration a patient's insulin sensitivity based on body weight.
  - It is labor-intensive to take into consideration previous insulin administration and food intake.
  - It can cause potentially dangerous hypoglycemia or hyperglycemia
- 11 Which of the following types of insulin therapy is recommended to meet prandial insulin needs?
- Basal therapy.
  - Bolus therapy.
  - Correction doses
  - Continuous infusion therapy.
- 12 Which of the following products is considered a basal insulin?
- Insulin aspart.
  - Insulin glargine
  - Insulin glulisine
  - Insulin lispro.
- 13 Insulin glargine is preferred to NPH insulin in the hospital setting because:
- It has a shorter duration of action.
  - It is a cloudy suspension, so it is not likely to be confused with insulins that are clear liquids
  - It has a lower risk of hypoglycemia
  - It has an early pronounced peak in glucose-lowering activity.
- 14 Rapid-acting insulins are preferred over regular insulin because of:
- The ability to modify the dose if a meal is only partially consumed.
  - The ability to add them to parenteral nutrient solutions for patients not eating meals
  - Their lower cost.
  - Their availability as clear liquids that do not require agitation before use.
- 15 In most diabetic patients with well-controlled blood glucose levels, the ratio of the total daily basal insulin dosage to the daily prandial insulin dosage is roughly:
- 1:2
  - 1:1.
  - 2:1.
  - 3:1.
- 16 Which of the following is an appropriate order when switching from a continuous i.v. insulin infusion to s.c. injections in a patient who is eating meals?
- Give a rapid-acting insulin s.c. immediately before stopping the infusion or long-acting insulin s.c. 2-3 hours before stopping the infusion.
  - Give a rapid- or short-acting insulin s.c. 1-2 hours after stopping the infusion and an intermediate- or long-acting insulin s.c. 2-3 hours before stopping the infusion.
  - Give a rapid- or short-acting insulin s.c. 1-2 hours before stopping the infusion and an intermediate- or long-acting insulin s.c. 2-3 hours after stopping the infusion.
  - Give a rapid- or short-acting insulin s.c. 1-2 hours after stopping the infusion and an intermediate- or long-acting insulin s.c. 2-3 hours after stopping the infusion.
- 17 A potential major benefit from the use of computer decision support systems to provide continuous variable rate i.v. insulin therapy is
- A reduction in nursing staff time.
  - A reduction in insulin dose requirements
  - A reduction in the risk of insulin infusion rate calculation error.
  - A reduction in the risk of hypoglycemia

18 Which of the following is an appropriate clinical performance measure for glycemic control programs in hospitals?

- The percentage of patients with a morning blood glucose value at the target level on the morning of hospitalization day 2
- The blood glucose concentration that constitutes an excessively high or low level and warrants alerting the physician.
- The criteria for considering a consultation with an endocrinologist or diabetes expert.
- The requirement for measuring A1C at the time of admission unless it was measured within the preceding month.

19 Algorithms for insulin correction doses as part of a standardized s.c. insulin order set are best based on the measured blood glucose concentration and:

- Nursing staff availability and convenience.
- Patient body weight or total daily insulin requirement as a measure of insulin sensitivity.
- Patient self-administration ability and convenience.
- Product availability and cost.

20 Strategies for cost justifying glycemic control initiatives based on amounts billed by physicians, nurse practitioners, physician assistants, and others that demonstrate a return-on-investment in providing clinical diabetes management services are referred to as:

- Bill-based.
- Hospital-based.
- Return-based.
- Self-supporting.

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