Management of Diabetes and Hyperglycemia in Hospitals

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Diabetes increases the risk for disorders that predispose individuals to hospitalization, including coronary artery, cerebrovascular and peripheral vascular disease, nephropathy, infection, and lower-extremity amputations. The management of diabetes in the hospital is generally considered secondary in importance compared with the condition that prompted admission. Recent studies (1,2) have focused attention to the possibility that hyperglycemia in the hospital is not necessarily a benign condition and that aggressive treatment of diabetes and hyperglycemia results in reduced mortality and morbidity. The purpose of this technical review is to evaluate the evidence relating to the management of hyperglycemia in hospitals, with particular focus on the issue of glycemic control and its possible impact on hospital outcomes. The scope of this review encompasses adult nonpregnant patients who do not have diabetic ketoacidosis or hyperglycemic crises.

For the purposes of this review, the following terms are defined (adapted from the American Diabetes Association [ADA] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus) (3):

- Medical history of diabetes: diabetes has been previously diagnosed and acknowledged by the patient's treating physician.
- Unrecognized diabetes: hyperglycemia (fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl) occurring during hospitalization and confirmed as diabetes after hospitalization by standard diagnostic criteria, but unrecognized as diabetes by the treating physician during hospitalization.
- Hospital-related hyperglycemia: hyperglycemia (fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl) occurring during the hospitalization that reverts to normal after hospital discharge.

What is the prevalence of diabetes in hospitals?

The prevalence of diabetes in hospitalized adult patients is not known. In the year 2000, 12.4% of hospital discharges in the U.S. listed diabetes as a diagnosis. The average length of stay was 5.4 days (4). Diabetes was the principal diagnosis in only 8% of these hospitalizations. The accuracy of using hospital discharge diagnosis codes for identifying patients with previously diagnosed diabetes has been questioned. Discharge diagnosis codes may underestimate the true prevalence of diabetes in hospitalized patients by as much as 40% (5,6). In addition to having a medical history of diabetes, patients presenting to hospitals may have unrecognized diabetes or hospital-related hyperglycemia. Umpierrez et al. (1) reported a 26% prevalence of known diabetes in hospitalized patients in a community teaching hospital. An additional 12% of patients had unrecognized diabetes or hospital-related hyperglycemia as defined above. Levetan et al. (6) reported a 13% prevalence of laboratory-documented hyperglycemia (blood glucose >200 mg/dl (11.1 mmol) in 1,034 consecutively hospitalized adult patients. Based on hospital chart review, 64% of patients with hyperglycemia had preexisting diabetes or were recognized as having new-onset diabetes during hospitalization. Thirty-six percent of the hyperglycemic patients remained unrecognized as having diabetes in the discharge summary, although diabetes or "hyperglycemia" was documented in

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Abbreviations: ADA, American Diabetes Association; AMI, acute myocardial infarction; CDE, certified diabetes educator; CHF, congestive heart failure; CK, creatinine kinase; CQI, continuous quality improvement; CRP, C-reactive protein; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DIGAMI, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; DSME, diabetes self-management education; DSWI, deep sternal wound infection; FFA, free fatty acid; GIK, glucose-insulin-potassium; ICAM, intercellular adhesion molecule; ICU, intensive care unit; IL, interleukin; IIT, intensive insulin therapy; JCAHO, Joint Commission of Accredited Hospital Organization; LIMP, lysosomal integral membrane protein; MCP, monocyte chemoattractant protein; MI, myocardial infarction; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NF, nuclear factor; NPO, nothing by mouth; PAI, plasminogen activator inhibitor; PCU, patient care unit; PKC, protein kinase C; PBMC, peripheral blood mononuclear cell; PMN, polymorphonuclear leukocyte; ROS, reactive oxygen species; TNF, tumor necrosis factor; TPN, total parenteral nutrition; UKPDS, U.K. Prospective Diabetes Study.

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

the progress notes for one-third of these patients.

Norhammar et al. (7) studied 181 consecutive patients admitted to the coronary care units of two hospitals in Sweden with acute myocardial infarction (AMI), no diagnosis of diabetes, and a blood glucose <200 mg/dl (<11.1 mmol/l) on admission. A standard 75-g glucose tolerance test was done at discharge and again 3 months later. The authors found a 31% prevalence of diabetes at the time of hospital discharge and a 25% prevalence of diabetes 3 months after discharge in this group with no previous diagnosis of diabetes.

Using the A1C test may be a valuable case-finding tool for identifying diabetes in hospitalized patients. Greci et al. (8) reported that an A1C >6% was 100% specific and 57% sensitive for identifying persons with diabetes in a small cohort of patients admitted through the emergency department of one hospital with a random blood glucose ≥126 mg/dl (7 mmol/l) and no prior history of diabetes.

From the patient's perspective, 24% of adult patients with known diabetes surveyed in 1989 reported being hospitalized at least once in the previous year (9). The risk for hospitalization increased with age, duration of diabetes, and number of diabetes complications. Persons with diabetes reported being hospitalized in the previous year three times more frequently compared with persons without diabetes. In summary, the prevalence of diabetes in hospitalized adults is conservatively estimated at 12.4–25%, depending on the thoroughness used in identifying patients.

WHAT IS THE LINK BETWEEN HIGH BLOOD GLUCOSE AND POOR OUTCOMES? POSSIBLE MECHANISMS

— The mechanism of harm from hyperglycemia on various cells and organ systems has been studied in in vitro systems and animal models. This research has centered on the immune system, mediators of inflammation, vascular responses, and brain cell responses.

Hyperglycemia and immune function

The association of hyperglycemia and infection has long been recognized, although the overall magnitude of the problem is still somewhat unclear (10,11). From a mechanistic point of view, the primary problem has been identified as phagocyte dysfunction. Studies have reported diverse defects in neutrophil and monocyte function, including adherence, chemotaxis, phagocytosis, bacterial killing, and respiratory burst (10–20). Bagdade et al. (14) were among the first to attach a glucose value to improvement in granulocyte function when they demonstrated significant improvement in granulocyte adherence as the mean fasting blood glucose was reduced from 293 ± 20 to 198 ± 29 mg/dl (16.3–11 mmol/l) in 10 poorly controlled patients with diabetes. Other investigators have demonstrated similar improvements in leukocyte function with treatment of hyperglycemia (17,21–23). In vitro trials attempting to define hyperglycemic thresholds found only rough estimates that a mean glucose >200 mg/dl (11.1 mmol/l) causes leukocyte dysfunction (13,14,16,24–26).

Alexiewicz et al. (17) demonstrated elevated basal levels of cytosolic calcium in the polymorphonuclear leukocytes (PMNs) of patients with type 2 diabetes relative to control subjects. Elevated cytosolic calcium was associated with reduced ATP content and impaired phagocytosis. There was a direct correlation between PMN cytosolic calcium and fasting serum glucose. These were both inversely proportional to phagocytic activity. Glucose reduction with glyburide resulted in reduced cytosolic calcium, increased ATP content, and improved phagocytosis.

Classic microvascular complications of diabetes are caused by alterations in the aldose reductase pathway, AGE pathway, reactive oxygen species pathway, and the protein kinase C (PKC) pathway (rev. in 27). Several of these pathways may contribute to immune dysfunction. PKC may mediate the effect of hyperglycemia on neutrophil dysfunction (28). Liu et al. (29) found that decreased phagocytic activity in diabetic mice correlated inversely with the formation of AGEs, although a direct cause-and-effect relationship was not proven. Ortmeyer and Mohsenin (30) found that hyperglycemia caused impaired superoxide formation along with suppressed activation of phospholipase D. Reduced superoxide formation has been linked to leukocyte dysfunction. Another recent study found a link among hyperglycemia, inhibition of glucose-6-phosphate dehydrogenase, and reduced superoxide production in isolated human neutrophils (31). Sato and colleagues (32–34) used chemiluminescence to evaluate neutrophil bactericidal function. The authors confirmed a relationship between hyperglycemia and reduced superoxide formation in neutrophils. This defect was improved after treatment with an aldose reductase inhibitor. This finding suggests that increased activity of the aldose reductase pathway makes a significant contribution to the incidence of diabetes-related bacterial infections.

Laboratory evidence of the effect of hyperglycemia on the immune system goes beyond the granulocyte. Nonenzymatic glycation of immunoglobulins has been reported (35). Normal individuals exposed to transient glucose elevation show rapid reduction in lymphocytes, including all lymphocyte subsets (36). In patients with diabetes, hyperglycemia is similarly associated with reduced T-cell populations for both CD-4 and CD-8 subsets. These abnormalities are reversed when glucose is lowered (37).

In summary, studies evaluating the effect of hyperglycemia on the immune system comprise small groups of normal individuals, patients with diabetes of various duration and types, and animal studies. These studies consistently show that hyperglycemia causes immunosuppression. Reduction of glucose by a variety of means reverses the immune function defects.

Hyperglycemia and the cardiovascular system

Acute hyperglycemia has numerous effects on the cardiovascular system. Hyperglycemia impairs ischemic preconditioning, a protective mechanism for ischemic insult (38). Concomitantly, infarct size increases in the setting of hyperglycemia. The same investigators demonstrated reduced coronary collateral blood flow in the setting of moderately severe hyperglycemia (39). Acute hyperglycemia may induce cardiac myocyte death through apoptosis (40) or by exaggerating ischemia-reperfusion cellular injury (41).

Other vascular consequences of acute hyperglycemia relevant to inpatient outcomes include blood pressure changes, catecholamine elevations, platelet abnormalities, and electrophysiologic changes. Streptozotocin-induced diabetes in rats results in significant hemodynamic

changes as well as QT prolongation (42). These changes were reversed with correction of hyperglycemia. In humans, Marfella et al. (43) reported increased systolic and diastolic blood pressure and increased endothelin levels with acute hyperglycemia in patients with type 2 diabetes. The same researchers also induced acute hyperglycemia (270 mg/dl or 15 mmol/l) over 2 h in healthy men. This produced elevated systolic and diastolic blood pressure, increased pulse, elevation of catecholamine levels, and QTc prolongation (44). Other investigators have demonstrated an association between acute hyperglycemia and increased viscosity, blood pressure (45), and natiuretic peptide levels (46).

Hyperglycemia and thrombosis

Multiple studies have identified a variety of hyperglycemia-related abnormalities in hemostasis, favoring thrombosis (47–51). For example, hyperglycemic changes in rats rapidly reduce plasma fibrinolytic activity and tissue plasminogen activator activity while increasing plasminogen activator inhibitor (PAI)-1 activity (52). Human studies in patients with type 2 diabetes have shown platelet hyperactivity indicated by increased thromboxane biosynthesis (47). Thromboxane biosynthesis decreases with reduction in blood glucose. Hyperglycemia-induced elevations of interleukin (IL)-6 levels have been linked to elevated plasma fibrinogen concentrations and fibrinogen mRNA (53,54).

Increased platelet activation as shown by shear-induced platelet adhesion and aggregation on extracellular matrix has been demonstrated in patients with diabetes (48). As little as 4 h of acute hyperglycemia enhances platelet activation in patients with type 2 diabetes (51). In this crossover, double-blind study, 12 patients were subjected to hyperglycemic (250 mg/dl, 13.9 mmol/l) and euglycemic (100 mg/dl, 5.55 mmol/l) clamps. Hyperglycemia precipitated stress-induced platelet activation as well as platelet P-selectin and lysosomal integral membrane protein (LIMP) expression. Hyperglycemia also caused increased plasma von Willebrand factor antigen, von Willebrand factor activity, and urinary 11-dehydro-thromboxane B_2 (a measure of thromboxane A_2 production). These changes were not seen in the euglycemic state.

If hyperglycemia-induced platelet hyperreactivity is particularly evident with high–shear stress conditions, as suggested in the above studies, this finding may explain the increased thrombotic events commonly seen in hospitalized patients with diabetes.

Hyperglycemia and inflammation

The connection between acute hyperglycemia and vascular changes likely involves inflammatory changes. Cultured human peripheral blood mononuclear cells (PBMCs), when incubated in high glucose medium (594 mg/dl, 33 mmol/l) for 6 h produce increased levels of IL-6 and tumor necrosis factor (TNF)-α (53). TNF-α is apparently involved in IL-6 production. Blocking TNF-α activity with anti-TNF monoclonal antibody blocks the stimulatory effect of glucose on IL-6 production by these cells. Other in vitro studies suggest that glucose-induced elevations in IL-6, TNF-α, and other factors may cause acute inflammation. This inflammatory response to glucose has been seen in adipose tissue, 3T3-L1 adipocyte cell lines, vascular smooth muscle cells, PBMCs, and other tissues or cell types (55–61).

In humans, moderate elevation of glucose to 270 mg/dl (15 mmol/l) for 5 h has been associated with increased IL-6, IL-18, and TNF-α (62). Elevations of these various inflammatory factors have been linked to detrimental vascular effects. For example, TNF-α extends the area of necrosis following left anterior descending coronary artery ligation in rabbits (63). In humans, TNF-α levels are elevated in the setting of AMI and correlate with severity of cardiac dysfunction (63,64). TNF-α may also play a role in some cases of ischemic renal injury and in congestive heart failure (CHF) (57,65). Ischemic preconditioning is associated with decreased postischemic myocardial TNF-α production (66). IL-18 has been proposed to destabilize atherosclerotic plaques, leading to acute ischemic syndromes (67).

One of the most commonly demonstrated relationships between hyperglycemia and inflammatory markers is the in vitro induction of the proinflammatory transcriptional factor, nuclear factor (NF)-κB by exposure of various cell types to 1–8 days of hyperglycemia (58,59,68–71). In patients with type 1 diabetes, activation of NF-κB in PBMCs was positively correlated to HbA_{1c} level ($r = 0.67$, $P < 0.005$) (72). A recent study by Schiefkofer et al. (73) demonstrated in vivo exposure to hyperglycemia (180 mg/dl, 10 mmol/l) for 2 h caused NF-κB activation.

Hyperglycemia and endothelial cell dysfunction

One proposed link between hyperglycemia and poor cardiovascular outcomes is the effect of acute hyperglycemia on the vascular endothelium. In addition to serving as a barrier between blood and tissues, vascular endothelial cells play a critical role in overall homeostasis. In the healthy state, the vascular endothelium maintains the vasculature in a quiescent, relaxant, antithrombotic, antioxidant, and antiadhesive state (rev. in 74,75). During illness the vascular endothelium is subject to dysregulation, dysfunction, insufficiency, and failure (76). Endothelial cell dysfunction is linked to increased cellular adhesion, perturbed angiogenesis, increased cell permeability, inflammation, and thrombosis. Commonly, endothelial function is evaluated by measuring endothelial-dependent vasodilatation, looking most often at the brachial artery. Human in vivo studies utilizing this parameter confirm that acute hyperglycemia to the levels commonly seen in the hospital setting (142–300 mg/dl or 7.9–16.7 mmol/l) causes endothelial dysfunction (77–82). Only one study failed to show evidence of endothelial cell dysfunction induced by short-term hyperglycemia (83). The degree of endothelial cell dysfunction after an oral glucose challenge was positively associated with the peak glucose level, ranging from 100 to 300 mg/dl (5.5–16.7 mmol/l) (78,79). Hyperglycemia may directly alter endothelial cell function by promoting chemical inactivation of nitric oxide (84). Other mechanisms include triggering production of reactive oxygen species (ROS) or activating other pathways (rev. in 27). Despite compelling experimental data, studies examining a possible association among hyperglycemia, endothelial function, and outcomes have not to date been done in hospitalized patients.

Hyperglycemia and the brain

Acute hyperglycemia is associated with enhanced neuronal damage following induced brain ischemia (85–98). Exploration of general mechanisms of

hyperglycemic damage has used various models of ischemia and various measures of outcomes. Models differ according to transient versus permanent ischemia as well as global versus localized ischemia. There is some indication from animal studies that irreversible ischemia or end arterial ischemia is not affected by hyperglycemia (87,99,100). The major portion of the brain that is sensitive to injury from hyperglycemia is the ischemic penumbra. This area surrounds the ischemic core. During evolution of the stroke, the ischemic penumbra may evolve into infarcted tissue or may recover as viable tissue (87,99,101,102). One of the primary mechanistic links between hyperglycemia and enhanced cerebral ischemic damage appears to be increased tissue acidosis and lactate levels associated with elevated glucose concentrations. This has been shown in various animal models with rare exception (94,102–108). Lactate has been associated with damage to neurons, astrocytes, and endothelial cells (104). In humans, Parsons et al. (109) demonstrated that the lactate-to-choline ratio determined by proton magnetic resonance spectroscopy (MRS) had value in predicting clinical outcomes and final infarct size in acute stroke. More recently, the same investigators used this method to demonstrate a positive correlation between glucose elevations and lactate production (110). Through this mechanism, hyperglycemia appears to cause hypoperfused at-risk tissue to progress to infarction.

Animal studies have shown additional association of hyperglycemia with various acute consequences that likely serve as intermediaries of adverse outcomes. For example, hyperglycemia causes accumulation of extracellular glutamate in the neocortex. Increased glutamate levels predict ensuing neuronal damage (95). A unique hippocampal cell culture model of "in vitro ischemia" demonstrated a similar relationship between hyperglycemia, glutamate activity, and increased intracellular calcium with enhanced cell death (98). Hyperglycemia has also been associated with DNA fragmentation, disruption of the blood-brain barrier, more rapid repolarization in severely hypoperfused penumbral tissue, β-amyloid precursor protein elevation, as well as elevated superoxide levels in neuronal tissue (111–115).

Many of the same factors noted earlier, linking hyperglycemia to cardiovascular event outcomes, likely contribute to acute cerebrovascular outcomes. Specifically, in brain ischemia models exposed to hyperglycemia, hydroxyl free radicals are elevated and positively correlate with tissue damage (116). Likewise, antioxidants have a neuroprotective effect (117). Elevated glucose levels have also been linked to inhibition of nitric oxide generation, increased IL-6 mRNA, decreased cerebral blood flow, and evidence of vascular endothelial injury (90,92,118,119). Again, the composite of evidence supports scientifically viable mechanisms of central nervous system injury from hyperglycemia in the acute setting.

Hyperglycemia and oxidative stress

Oxidative stress occurs when the formation of ROS exceeds the body's ability to metabolize them. Attempts to identify a unifying basic mechanism for many of the diverse effects of acute hyperglycemia point to the ability of hyperglycemia to produce oxidative stress (58,69,120). Acute experimental hyperglycemia to levels commonly seen in hospitalized patients induces ROS generation. Endothelial cells exposed to hyperglycemia in vitro switch from producing nitric oxide to superoxide anion (84). Increased ROS generation causes activation of transcriptional factors, growth factors, and secondary mediators. Through direct tissue injury or via activation of these secondary mediators, hyperglycemia-induced oxidative stress causes cell and tissue injury (58,59,62,70,72,74,80,121–127). In all cases studied, abnormalities were reversed by antioxidants or by restoring euglycemia (58,59,70,72,80,122,127).

Is insulin per se therapeutic?

Two large, well-done prospective studies support the relationship between insulin therapy and improved inpatient outcomes (2,128). The prevalent assumption has been that insulin attained this benefit indirectly by controlling blood glucose. However, a growing body of literature raises the question of whether insulin may have direct beneficial effects independent of its effect on blood glucose (121,129–132).

Multiple studies suggest cardiac and neurological benefits of glucose-insulin-potassium (GIK) infusions (133–154). One may propose that such therapy supports a direct effect of the insulin since blood glucose control is not the goal of these infusions and the benefits have been displayed in normal humans and animals. Although the direct effect of insulin may play a significant role in benefits of GIK therapy, other metabolic factors are likely to be major contributors to the mechanism of this therapy. The theory promoting this form of therapy centers on the imbalance between low glycolytic substrate in the hypoperfused tissue and elevated free fatty acids (FFAs) mobilized through catecholamine-induced lipolysis (41,155–159). In ischemic cardiac tissue, there is decreased ATP and increased inorganic phosphate production (148,156,159). Adequate glycolytic ATP is important for maintaining cellular membranes, myocardial contractility, and avoidance of the negative effect of fatty acids as substrate for ischemic myocardium (155,158–161). FFAs are associated with cardiac sympathetic overactivity, worsened ischemic damage, and possibly arrhythmias. Accordingly, using a model of 60-min low-flow ischemia followed by 30 min of reperfusion in rat hearts, investigators have demonstrated the ability of GIK infusion to increase glycolysis, decrease ATP depletion, and maintain lower inorganic phosphate levels in the affected tissue (148). These effects extrapolated to improved systolic and diastolic function in this model. In other animal models, GIK infusion in improved left ventricular contractility, decreased tissue acidosis, and decreased infarct size (144,152,162).

In small studies of individuals with or without diabetes undergoing coronary artery bypass surgery, GIK therapy is associated with shorter length of intubation and shorter length of stay (142,143,163). As therapy for patients with an AMI, GIK therapy is associated with the expected decrease in FFAs, decreased heart failure, and a suggestion of improved short-term survival (133–135,139,164). In follow-up of a first myocardial infarction (MI), individuals who received GIK therapy reported better stress tolerance, an elevated ischemic threshold, and improved myocardial perfusion by 99 *m*-Tc-tetrofosmin–gated single photon emission computed tomography (SPECT) compared with those receiving saline infusion (149). These studies of classic GIK therapy with emphasis on glucose delivery have been small and more suggestive than conclusive. No large, randomized, placebo-controlled studies have been reported. Even less information is available

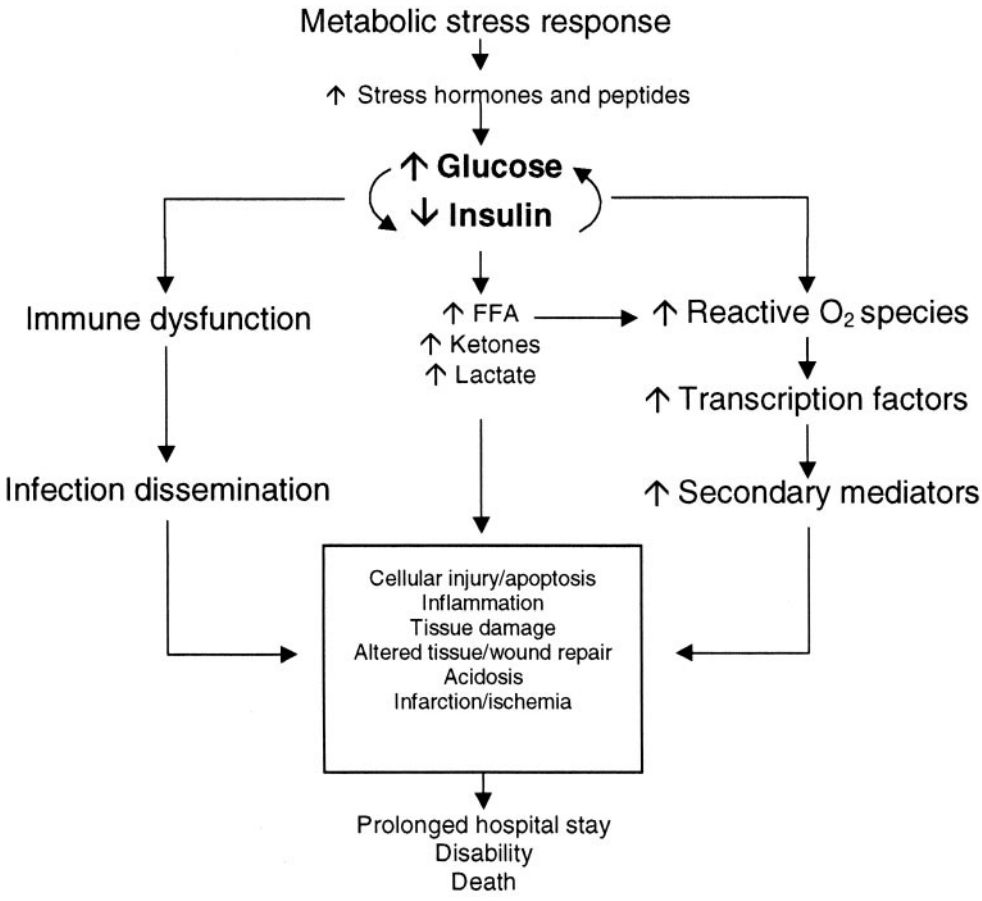

Figure 1—*Link between hyperglycemia and poor hospital outcomes. Hyperglycemia and relative insulin deficiency caused by metabolic stress triggers immune dysfunction, release of fuel substrates, and other mediators such as ROS. Tissue and organ injury occur via the combined insults of infection, direct fuel-mediated injury, and oxidative stress and other downstream mediators. See text for details.*

regarding the use of GIK therapy in strokes or cerebral ischemia. Limited studies have demonstrated safety of GIK therapy in the acute stroke patient, with a trend to reduced mortality, and a decrease in blood pressure (147,150). However, the data are clearly inadequate to make any conclusions of benefit.

Beyond GIK therapy, one finds increasing support for a direct effect of insulin on many of the abnormalities that underlie inpatient complications. Insulin treatment, ranging in duration from brief euglycemic-hyperinsulinemic clamps to 2 months of ongoing therapy, improves endothelial cell function (165–171). There are rare exceptions to this finding (172). Insulin also has vasodilatory properties in the internal carotid and femoral arteries (165,167). The vasodilatory properties of insulin appear to be mediated at least in part by stimulating nitric oxide release (165,166). Aortic endothelial cell cultures have also demonstrated insulin-induced nitric oxide synthase activity and increased nitric oxide levels (172,173). In a rat model, insulin inhibits the upregulation of the endothelial adhesion molecule P-selectin expression seen as a consequence of elevated glucose levels (121).

Insulin infusion has anti-inflammatory effects (129,174,175). In a large study of intensive insulin infusion therapy in the intensive care unit, investigators found decreased C-reactive protein (CRP) levels in insulin-treated patients (176). Cell culture studies have shown the ability of insulin incubation to reduce oxidative stress and its associated apoptosis in cardiomyocytes (177). In addition to the induction of endothelial-derived nitric oxide, human aorta cell and human mononuclear cell culture studies have shown dose-dependent reductions in ROS, the proinflammatory transcription factor NF-κB, intercellular adhesion molecule (ICAM)-1, and the chemokine monocyte chemoattractant protein (MCP)-1 (173,178–180). Insulin also inhibits the production TNF-α and the proinflammatory transcription factor early growth response gene (Egr)-1 (181). These effects suggest a general anti-inflammatory action of insulin.

In an animal model of myocardial ischemia, insulin given early in the acute insult reduced infarct size by >45% (182). This effect was mediated through the Akt and p70s6 kinase–dependent signaling pathway and was independent of glucose. There is preliminary evidence of insulin's ability to improve pulmonary diffusion and CHF in humans (183). Studies have also suggested that insulin protects from ischemic damage in the brain, kidney, and lung (184–186). In catabolic states such as severe burns, hyperglycemia promotes muscle catabolism, while exogenous insulin produces an anabolic effect (187). Insulin therapy has also been associated with an improved fibrinolytic profile in patients at the time of acute coronary events, reducing fibrinogen and PAI-1 levels (132). Finally, insulin infusion reduces collagen-induced platelet aggregation and several other parameters of platelet activity in humans. This effect was attenuated in obese individuals (188).

In summary, the overwhelming balance of evidence supports a beneficial effect of insulin in the acute setting. Whether these benefits are the result of a direct pharmacologic effect of insulin or represent an indirect effect by improved glucose control, enhanced glycolysis, or suppressed lipolysis is more difficult to determine. Studies in cell cultures control for glucose but have other physiologic limitations. Nevertheless, the data are provocative and certainly leave the impression that insulin therapy in the hospital has significant potential for benefit. Considering the numerous contraindications to the use of oral agents in the hospital, insulin is the clear choice for glucose manipulation in the hospitalized patient.

Potential relationships between metabolic stress, hyperglycemia, hypoinsulinemia, and poor hospital outcomes

To explain the dual role of glucose and insulin on hospital outcomes, Levetan and Magee (189) proposed the following relationships. Elevations in counterregularory hormones accelerate catabolism, hepatic gluconeogenesis, and lipolysis. These events elevate blood glucose, FFAs, ketones, and lactate. The rise in glucose blunts insulin secretion via the mechanism of glucose toxicity (190), resulting in further hyperglycemia. The vicious cycle of stress-induced hyperglycemia and hypoinsulinemia subsequently causes maladaptive responses in immune function, fuel production, and synthesis of mediators that cause further tissue and organ dysfunction (Fig. 1). Thus, the combination of hyperglycemia and relative hypoinsulinemia is mechanistically positioned to provide a plausible explanation for the poor hospital outcomes seen in observational studies.

WHAT ARE THE TARGET BLOOD GLUCOSE LEVELS FOR THE HOSPITALIZED PATIENT?

A rapidly growing body of literature supports targeted glucose control in the hospital setting with potential for improved mortality, morbidity, and health care economic outcomes. The relationship of hospital outcomes to hyperglycemia has been extensively examined. Hyperglycemia in the hospital may result from stress, decompensation of type 1 diabetes, type 2 diabetes, or other forms of diabetes and/or may be iatrogenic due to administration of pharmacologic agents, including glucocorticoids, vasopressors, etc. Distinction between decompensated diabetes and stress hyperglycemia is often not made or alternatively is not clear at the time of presentation with an acute illness. When hyperglycemia is treated along with other acute problems, outcomes are generally improved. This section will review the evidence for outcomes from observational and interventional studies in hospitalized patients with hyperglycemia. While observational reports abound, interventional studies that report improved outcomes with targeted glucose control—though few in number—are now beginning to provide a source of evidence in the literature.

To make the case for defining targets for glucose control in hospital settings, it is necessary to examine the literature on both short- and long-term mortality. Data regarding diabetes and hyperglycemia-associated morbidity have emerged from specific clinical settings. These data include infection rates, need for intensive care unit admission, functional recovery, and health economic outcomes such as length of stay and hospital charges. For their practical implications and for the purpose of this review, literature on the association of blood glucose level with outcomes will be grouped into the medical and surgical areas in which studies have been reported as follows: general medicine and surgery, cardiovascular disease (CVD) and critical care, and neurologic disorders (Table 1).

General medicine and surgery

Observational studies suggest an association between hyperglycemia and increased mortality. Recently, investigators have reported on outcomes correlated with blood glucose levels in the general medicine and surgery setting. Pomposelli et al. (191) studied 97 patients with diabetes undergoing general surgery procedures. Blood glucose testing occurred every 6 h. The authors found that a single blood glucose level >220 mg/dl (12.2 mmol/l) on the first postoperative day was a sensitive (85%), but relatively nonspecific (35%), predictor of nosocomial infections. Patients with a blood glucose value(s) >220 mg/dl (12.2 mmol/l) had infection rates that were 2.7 times higher than the rate for patients with blood glucose values <220 mg/dl (12.2 mmol/l). When minor infections of the urinary tract were excluded, the relative risk (RR) for serious postoperative infection, including sepsis, pneumonia, and wound infections, was 5.7.

Umpierrez et al. (1) reviewed 1,886 admissions for the presence of hyperglycemia (fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl on two or more occasions). Care was provided on general medicine and surgery units. Among these subjects, there were 223 patients (12%) with new hyperglycemia and 495 (26%) with known diabetes. Admission blood glucose for the normoglycemic group was 108 ± 10.8 mg/dl (6 ± 0.6 mmol/l); for the new hyperglycemia group, it was 189 ± 18 mg/dl (10.5 ± 1 mmol/l); and for known diabetes, it was 230.4 ± 18 mg/dl (12.8 ± 1 mmol/l). After adjusting for confounding factors, patients with new hyperglycemia had an 18-fold increased inhospital mortality and patients with known diabetes had a 2.7-fold increased inhospital mortality compared with normoglycemic patients. Length of stay was higher for the new hyperglycemia group compared with normoglycemic and known diabetic patients (9 ± 0.7, 4.5 ± 0.1, and 5.5 ± 0.2 days, respectively, $P < 0.001$). Both the new hyperglycemia and known diabetic patients were more likely to require intensive care unit (ICU) care when compared with normoglycemic subjects (29 vs. 14 vs. 9%, respectively, $P < 0.01$) and were more likely to require transitional or nursing home care. There was a trend toward a higher rate of infections and neurologic events in the two groups with hyperglycemia (1). It is likely that the "new" hyperglycemic patients in this report were a heterogeneous population made up of patients with unrecognized diabetes, prediabetes, and/or stress hyperglycemia secondary to severe illness.

The observational data from these two studies suggest that hyperglycemia from any etiology in the hospital on general medicine and surgery services is a significant predictor of poor outcomes, relative to outcomes for normoglycemic subjects. Patients with hyperglycemia, with or without diabetes, had increased risk of inhospital mortality, postoperative infections, neurologic events, intensive care unit admission and increased length of stay. The Pomposelli article (191) found that a blood glucose level of 220 mg/dl (12.2mmol/l) separated patients for risk of infection. Data from the

Table 1—*Evidence for association of blood glucose level with clinical outcomes*

Clinical setting	Threshold BG levels [mg/dl, (mmol/l)]	Outcomes and comments
General medicine and surgery	Mortality, ICU admits, length of stay, and nursing home or transitional care admits correlated with BG and glucose tolerance status: Normoglycemia = 108 ± 10.8 (6 ± 0.6); New hyperglycemia = 189 ± 18 (10.5 ± 1); Known diabetes = 230.4 ± 18 (12.8 ± 1).	Review of BG levels of patients on general medicine and surgery wards. Hyperglycemia defined as two or more measurements with fasting BG ≥126 (7) and/or random ≥200 (11.1). Hospital mortality for normoglycemic patients was 1.7%. With known diabetes mortality was 3% and with "new" hyperglycemia it was 16%. After adjustment for variables, the "new" hyperglycemia group had an 18.3-fold increased mortality rate compared with a 2.7-fold increase with known diabetes. Patients with new hyperglycemia also had an increased length of stay, were more likely to require ICU care, and were more likely to require transitional or nursing home care (Obs, *n* = 1,886) (1).
	Infection rates correlated with BG above 220.	5.9-fold increase in serious infections, including sepsis, pneumonia, and wound infections for BG over 220 (12.2), which was a sensitive (85%) predictor of nosocomial infection (Obs, *n* = 97) (191).
CVD and critical care		
Acute MI	Mortality, CHF, and cardiogenic shock risk correlated with BG Above 109.8 (6), in patients without known diabetes; At or above 124 (6.9), with diabetes diagnosis.	Literature review. Relative risk (RR) for inhospital mortality increased 3.9-fold in subjects without diabetes with BG at or above range of 109.8–144 (6.1–8), 95% CI 2.9–5.4; risk of CHF and cardiogenic shock was also increased. RR for moderate increase in mortality with known diabetes with was 1.7 (14 article review with meta-analysis) (192).
	Admit BG, stratified according to WHO criteria and correlated with mortality: I. BG less than 100.8 (5.6) to IV. BG greater than or equal to 199.8 (11)	One-year mortality was 19.3% for BG <100.8 (5.6) at time of admission, compared with 44% when BG ≥199.8 (11). Mortality was higher in patients with diabetes than in those without (40 vs. 16%, $P < 0.05$) (Obs, *n* = 336) (193).
	Mortality correlated with BG in intensive insulin therapy group where mean BG = 172.8 ± 59.4 (9.6 ± 3.3) compared with conventional therapy group where mean BG = 210.6 ± 73.8 (11.7 ± 4.1).	Intensive insulin therapy in patients with acute MI, followed by multishot regimen for 3 or more months, with 29% reduction in mortality at 1 year. Benefit extends to at least 3.4 years. One life saved for nine patients treated (Int, *n* = 620) (128).
Cardiac surgery	Mortality positively correlated with BG in a dose-dependent manner, with the lowest mortality in the group where mean postoperative BG <150 (8.3).	Observational studies using historical controls. Both mortality and incidence of DSWIs were reduced to the nondiabetic range after implementing insulin infusion protocols with progressively lower BG targets over time (196,197).
Critical care	Mortality and sepsis risk correlated with BG. Intensive insulin therapy arm with mean BG 103 ± 19 (5.7 ± 1.06); conventional treatment arm with mean BG 153 ± 33 (8.5 ± 1.8).	Prospective randomized controlled study of adults admitted to surgical ICU and on mechanical ventilation. Sixty percent had had cardiac surgery, majority of others also surgical patients. IIT to maintain BG in 80–110 (4.4–6.1) range compared with conventional therapy (CT) to target BG to 180–200 (10–11.1). IIT reduced ICU mortality by 40% from 8.0 to 4.6%, $P < 0.04$. For each 20 mg/dl increase in BG, risk of death was increased by 30%. IIT also reduced incidence of sepsis by 46% and overall hospital mortality by 34%. A gradual decline in risk for ICU and hospital death with decline in BG level was observed, with no identifiable threshold below which there was no further risk reduction. Prolonged inflammation, defined as elevation in CRP above 150 mg/dl for over 3 days, was associated with mean BG level (per 20 mg/dl added) with or of 1.16 (95% CI 1.06–1.24), $P = 0.0006$. Threshold may be higher than 110 (6.1) (Int, *n* = 1,548) (2,200).
Neurologic disorders		
Acute stroke	Mortality and functional recovery after acute ischemic stroke correlated with BG. Admission BG over 110 (6.1) for mortality; over 121 for functional recovery.	Literature review (1966–2000). After ischemic stroke, admission glucose level >110–126 (>6.1–7) associated with increased risk of in hospital or 30-day mortality in patients without diabetes only (RR 3.8; 95% CI 2.32–4.64). Stroke survivors without diabetes and BG over 121–144 (6.7–8) had RR of 1.41 (1.16–1.73) for poor functional recovery (metaanalysis, 26 studies) (96).
	Neurologic function after acute stroke correlated with admission BG. Odds for neurologic improvement decreased with OR of 0.76 for each 100 mg/dl BG increase.	Controlled, randomized trial of molecular heparin in acute stroke. Mean admission BG 144 ± 68 (8 ± 3.8) associated with neurologic improvement at 3 months. In those without improvement, BG was 160 ± 84 (8.9 ± 4.7). As BG increased, odds for neurologic improvement decreased, with OR = 0.76 per 100-mg/dl increase in admission BG (95% CI 0.61–0.95, $P = 0.01$) (Obs, *n* = 1,259) (201).
	Functional outcomes and return to work after stroke correlated with admission BG. Admission BG under 120 (6.7) with positive relationship.	Prospective data. Stroke-related deficits were more severe when admission glucose values were >120 (6.7). Only 43% of patients with an admission glucose value of >120 mg/dl able to return to work, whereas 76% of patients with lower glucose values regained employment (202).
	RtPA-induced hemorrhage into an infarct correlated with BG over 300 (16.7).	Central collection of retrospective and prospective data on acute ischemic stroke treated in clinical practices with alteplase. BG >300 mg/dl an independent risk factor for hemorrhage into an infarct when treatment with recombinant RtPA is given (Obs, *n* = 1,205) (203).
	Mortality, length of stay, and charges increased with admission BG ≥130 (7.2).	Hospitalization for acute ischemic stroke. Hyperglycemia (random BG at or above 130) present in 40% at admission. Most remained hyperglycemic with mean BG values of 206 (11.4). Random admission serum glucose ≥130 (7.2) independently associated with increased risk of death at 30 days (HR 1.87) and 1 year (HR 1.75), both $P \leq 0.01$. Other significant correlates with hyperglycemia, when compared with normal BG, were length of stay (7 vs. 6 days, $P = 0.015$) and charges ($5,262 vs. $6,611, $P < 0.001$) (Obs, *n* = 656) (205).
	Hypoglycemia risk and 4 week mortality with BG targeted to 72–126 (4–7).	Glucose-insulin infusion in acute stroke with mild-to-moderate hyperglycemia. Examined the safety of treating to a target glucose of 72–126 (4–7). Lowering BG was found to be without significant risk of hypoglycemia or 4-week excess mortality in patients with acute stroke and mild-to-moderate hyperglycemia (147).
	Penumbral salvage, final infarct size, and functional outcome in patients with median acute BG ranging from 104.4 to 172.8 (5.8–9.6).	Study of MRI and MRS in acute stroke. Prospective evaluation with serial diffusion-weighted and perfusion-weighted MRI and acute BG measurements. Median acute BG was 133.2 mg/dl (7.4 mmol/l), range 104.4–172.8 mg/dl (5.8–9.6 mmol/l). A doubling of BG from 5 to 10 mmol/l led to a 60% reduction in penumbral salvage and a 56-cm^3 increase in final infarct size. In patients with acute perfusion-diffusion mismatch, acute hyperglycemia was also correlated with reduced salvage of mismatch tissue from infarction, greater final infarct size, and worse functional outcome, independent of baseline stroke severity, lesion size, and diabetic status (Obs, *n* = 63) (110).

BG, blood glucose; CT, conventional therapy; DM, diabetes mellitus; HR, hazard ratio; Int, interventional study; Obs, observational study; RtPA, recombinant tissue plasminogen activator; Rx, therapy.

Umpierrez study (1) and most of the literature from other disciplines, as outlined elsewhere in this review, would suggest a lower threshold for optimal hospital outcomes.

Evidence for a blood glucose threshold. The Umpierrez study demonstrated better outcomes for patients with fasting and admission blood glucose <126 mg/dl (7 mmol/l) and all random blood glucose levels <200 mg/dl (11.1 mmol/l). Because the Pomposelli and Umpierrez studies are observational, a causal link between hyperglycemia and poor outcomes cannot be established.

CVD and critical care

Numerous articles contain data linking blood glucose level to outcomes in AMI and cardiac surgery, for which patients receive care predominantly in the ICU setting. The majority of these trials are observational, but the literature also includes several large, landmark interventional studies that have markedly increased awareness of the need for targeted glycemic control in these settings.

AMI. In 2000, Capes et al. (192) reviewed blood glucose levels and mortality in the setting of AMI from 15 previously published studies and performed a meta-analysis of the results to compare the RR of in-hospital mortality and CHF in both hyper- and normoglycemic patients with and without diabetes. In subjects without known diabetes whose admission blood glucose was ≥109.8 mg/dl (6.1 mmol/l), the RR for in-hospital mortality was increased significantly (RR 3.9, 95% CI 2.9–5.4). When diabetes was present and admission glucose was ≥180 mg/dl (10 mmol/l), risk of death was moderately increased (1.7, 1.2–2.4) compared with patients who had diabetes but no hyperglycemia on admission.

Bolk et al. (193) analyzed admission blood glucose values in 336 prospective, consecutive patients with AMI with average follow-up to 14.2 months. Twelve percent of this cohort had previously diagnosed diabetes. Multivariate analysis revealed an independent association of admission blood glucose and mortality. The 1-year mortality rate was 19.3% in subjects with admission plasma glucose <100.8 mg/dl (5.6 mmol/l) and rose to 44% with plasma glucose ≥199.8 mg/dl (11 mmol/l). Mortality was higher in patients with known diabetes than in those without diabetes (40 vs. 16%, $P < 0.05$.).

From the frequently cited Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, Malmberg and colleagues (128,194) have published the results of a prospective interventional trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with AMI, reporting mortality at 1 year. Of 620 persons with diabetes and AMI, 306 were randomized to intensive treatment with insulin infusion therapy, followed by a multishot insulin regimen for 3 or more months. Patients randomized to conventional therapy received standard diabetes therapy and did not receive insulin unless clinically indicated. Baseline blood glucose values were similar in the intensive treatment group, 277.2 ± 73.8 mg/dl (15.4 ± 4.1 mmol/l), and the conventional treatment group, 282.6 ± 75.6 mg/dl (15.7 ± 4.2 mmol/l). Blood glucose levels decreased in the first 24 h in the intervention group to 172.8 ± 59.4 mg/dl (9.6 ± 3.3 mmol/l; $P < 0.001$ vs. conventional treatment), whereas blood glucose declined to 210.6 ± 73.8 mg/dl (11.7 ± 4.1mmol/l). The blood glucose range for each group was wide: 116.4–232.2 mg/dl (6.5–12.9 mmol/l) in the intensive treatment group and 136.8–284.4 mg/dl (7.6–15.8 mmol/l) in the conventional treatment group. Mortality at 1 year in the intensive treatment group was 18.6%, and for the conventional treatment group it was 26.1%, a 29% reduction in mortality for the intervention arm ($P = 0.027$). At 3.4 (1.6–5.6) years follow-up, mortality was 33% in the intensive treatment group and 44% in the conventional treatment group (RR 0.72, 95% CI 0.55–0.92; $P = 0.011$), consistent with persistent reduction in mortality. The benefit of intensive control was most pronounced in 272 patients who had not had prior insulin therapy and had a less risk for CVD (0.49, 0.30–0.80; $P = 0.004$).

In the DIGAMI study, insulin infusion in AMI followed by intensive subcutaneous insulin therapy for 3 or more months improved long-term survival, with a benefit that extends to at least 3.4 years (128). An absolute reduction in mortality of 11% was observed, meaning that one life was saved for every nine treated patients. The observation that higher mean glucose levels were associated with increased mortality between groups of patients with diabetes would suggest that stress hyperglycemia plays an independent role in the determination of outcomes. In addition, it is of interest that in spite of the observation that blood glucose levels between the intensive and conventional treatment groups were similar, a significant difference in mortality between these groups was found. A relatively modest reduction in blood glucose in the intensive treatment group compared with the conventional treatment group produced a statistically significant improvement in mortality. This suggests the possibility that the beneficial effect of improved control may be mediated through mechanisms other than a direct effect of hyperglycemia, such as a direct effect of insulin.

Evidence for a blood glucose threshold for increased mortality in AMI.

- The metaanalysis of Capes et al. (192) reported a blood glucose threshold of >109.8 mg/dl (6.1 mmol/l) for patients without diabetes and >180 mg/dl (10 mmol/l) for known diabetes.
- The observational study of Bolk et al. (193) identified threshold blood glucoses, divided by World Health Organization (WHO) classification criteria, with mortality risk of 19.3% for normoglycemia (blood glucose <100.8 mg/dl [5.6 mmol/l]), which rose progressively to 44% for blood glucose >199.8 mg/dl (11 mmol/l).
- In the DIGAMI study, mean blood glucose in the intensive insulin intervention arm was 172.8 mg/dl (9.6 mmol/l), where lower mortality risk was observed. In the conventional treatment arm, mean blood glucose was 210.6 mg/dl (11.7 mmol/l). The broad range of blood glucose levels within each arm limits the ability to define specific blood glucose target thresholds.

Cardiac surgery. Attainment of targeted glucose control in the setting of cardiac surgery is associated with reduced mortality and risk of deep sternal wound infections. Furnary and colleagues (196,197) treated cardiac surgery patients with diabetes with either subcutaneous insulin (years 1987–1991) or with intravenous insulin (years 1992–2003) in the perioperative period. From 1991–1998, the target glucose range was 150−200 mg/dl (8.3–11.1 mmol/l); in 1999 it was dropped to 125–175 mg/dl (6.9–9.7 mmol/l), and in 2001 it was again lowered to 100–150 mg/dl (5.5–8.3 mmol/l). Following implementation of the protocol in 1991, the authors re-

ported a decrease in blood glucose level for the first 2 days after surgery and a concomitant decrease in the proportion of patients with deep wound infections, from 2.4% (24 of 990) to 1.5% (5 of 595) ($P < 0.02$) (198). A recent analysis or the cohort found a positive correlation between the average postoperative glucose level and mortality, with the lowest mortality in patients with average postoperative blood glucose <150 mg/dl (8.3 mmol/l) (197).

Golden et al. (199) performed a nonconcurrent prospective cohort chart review study in cardiac surgery patients with diabetes ($n = 411$). Perioperative glucose control was assessed by the mean of six capillary blood glucose measures performed during the first 36 h following surgery. The overall infectious complication rate was 24.3%. After adjustment for variables, patients with higher mean capillary glucose readings were at increased risk of developing infections. Compared with subjects in the lowest quartile for blood glucose, those in quartiles 2–4 were at progressively increased risk for infection (RR 1.17, 1.86, and 1.78 for quartiles 2, 3, and 4, respectively, $P = 0.05$ for trend). These data support the concept that perioperative hyperglycemia is an independent predictor of infection in patients with diabetes.

Critical care. Van den Berghe et al. (200) performed a prospective, randomized controlled study of 1,548 adults who were admitted to a surgical intensive care unit and were receiving mechanical ventilation. Reasons for ICU admission were cardiac surgery (~60%) and noncardiac indications, including neurologic disease (cerebral trauma or brain surgery), other thoracic surgery, abdominal surgery or peritonitis, vascular surgery, multiple trauma, or burns and transplant (4–9% each group). Patients were randomized to receive intensive insulin therapy (IIT) to maintain target blood glucose in the 80–110 mg/dl (4.4–6.1) range or conventional therapy to maintain target blood glucose between 180 and 200 mg/dl (10–11.1 mmol/l). Insulin infusion was initiated in the conventional treatment group only if blood glucose exceeded 215 mg/dl (11.9 mmol/l), and the infusion was adjusted to maintain the blood glucose level between 180 and 200 mg/dl (10.0 and 11.1 mmol/l). After the patients left the ICU they received standard care in the hospital with a target blood glucose of 180 and 200 mg/dl (10.0 and 11.1 mmol/l).

Ninety-nine percent of patients in the IIT group received insulin infusion, as compared with 39% of the patients in the conventional treatment group. In the IIT arm, blood glucose levels were 103 ± 19 mg/dl (5.7 ± 1.1 mmol/l) and in conventional treatment 153 ± 33 mg/dl (8.5 ± 1.8 mmol/l). IIT reduced mortality during ICU care from 8.0% with conventional treatment to 4.6% ($P < 0.04$). The benefit of IIT was attributable to its effect on mortality among patients who remained in the unit for more than 5 days (20.2% with conventional treatment vs. 10.6% with IIT, $P = 0.005$). IIT also reduced overall inhospital mortality by 34% (2). In a subsequent analysis, Van den Berghe (200) demonstrated that for each 20 mg/dl (1.1 mmol/l), glucose was elevated >100 mg/dl (5.5 mmol/l) and the risk of ICU death increased by 30% ($P < 0.0001$). Daily insulin dose (per 10 units added) was found as a positive rather than negative risk factor, suggesting that it was not the amount of insulin that produced the observed reduction in mortality. Hospital and ICU survival were linearly associated with ICU glucose levels, with the highest survival rates occurring in patients achieving an average blood glucose <110 mg/dl (6.1 mmol). An improvement in outcomes was found in patients who had prior diabetes as well as in those who had no history of diabetes.

Evidence for a blood glucose threshold in cardiac surgery and critical care.

- Furnary et al. (196) and Zerr et al. (198) identified a reduction in mortality throughout the blood glucose spectrum with the lowest mortality in patients with blood glucose <150 mg/dl (8.3 mmol/l).
- Van den Berghe et al. (2), using intensive intravenous insulin therapy, reported a 45% reduction in ICU mortality with a mean blood glucose of 103 mg/dl (5.7 mmol/l), as compared with the conventional treatment arm, where mean blood glucose was 153 mg/dl (8.5 mmol/l) in a mixed group of patients with and without diabetes.

Acute neurologic illness and stroke. In the setting of acute neurologic illness, stroke, and head injury, data support a weak association between hyperglycemia and increased mortality and are scanty for patients with known diabetes. In these clinical settings, available data, with one exception, are observational. Capes et al. (96) reported on mortality after stroke in relation to admission glucose level from 26 studies, published between 1996 and 2000, where RRs for prespecified outcomes were reported or could be calculated. After ischemic stroke, admission glucose level >110–126 mg/dl (>6.1–7 mmol/l) was associated with increased risk of inhospital or 30-day mortality in patients without diabetes only (RR 3.8, 95% CI 2.32–4.64). Stroke survivors without diabetes and blood glucose >121–144 mg/dl (6.7–8 mmol/l) had an RR of 1.41 (1.16–1.73) for poor functional recovery. After hemorrhagic stroke, admission hyperglycemia was not associated with higher mortality in either the diabetes or nondiabetes groups.

Several of the studies that were included in the analysis of Capes et al. (96) contain additional data that support an association between blood glucose and outcomes in stroke. In the Acute Stroke Treatment Trial (TOAST), a controlled, randomized study of the efficacy of a low–molecular weight heparinoid in acute ischemic stroke ($n = 1,259$), neurologic improvement at 3 months (a decrease by four or more points on the National Institutes of Health [NIH] Stroke Scale or a final score of 0) was seen in 63% of subjects. Those with improvement had a mean admission glucose of 144 ± 68 mg/dl, and those without improvement had blood glucose of 160 ± 84 mg/dl. In multivariate analysis, as admission blood glucose increased, the odds for neurologic improvement decreased with an OR of 0.76 per 100 mg/dl increase in admission glucose (95% CI 0.61–0.95, $P = 0.01$) (201). Subgroup analysis for patients with or without a history of diabetes was not done. Pulsinelli et al. (202) reported worse outcomes for both patients with diabetes and hyperglycemic patients without an established diagnosis of diabetes compared with those who were normoglycemic. Stroke-related deficits were more severe when admission glucose values were >120 mg/dl (6.7 mmol/l). Only 43% of the patients with an admission glucose value of >120 mg/dl were able to return to work, whereas 76% of patients with lower glucose values regained employment.

Demchuk et al. (203) studied the effect of admission glucose level and risk for intracerebral hemorrhage into an infarct

when treatment with recombinant tissue plasminogen activator was given to 138 patients presenting with stroke. Twenty-three percent of the cohort had known diabetes. The authors reported admission blood glucose and/or history of diabetes as the only independent predictors of hemorrhage. Kiers et al. (204) prospectively studied 176 sequential acute stroke patients and grouped them by admission blood glucose level, HbA_{1c} level, and history of diabetes. Threshold blood glucose for euglycemia was defined as fasting blood glucose <140 mg/dl (7.8 mmol/l). The authors divided patients into one of four groups: euglycemia with no history of diabetes, patients with "stress hyperglycemia" (blood glucose >140 mg/dl, 7.8 mmol/l, and HbA_{1c} <8%), newly diagnosed diabetes (blood glucose >140 mg/dl, 7.8 mmol/l, and HbA_{1c} >8%), and known diabetes. No difference was found in the type or site of stroke among the four groups. Compared with the euglycemic, nondiabetic patients, mortality was increased in all three groups of hyperglycemic patients.

Williams et al. (205) reported on the association of hyperglycemia and outcomes in a group of 656 acute stroke patients. Fifty-two percent of the cohort had a known history of diabetes. Hyperglycemia, defined as a random blood glucose ≥130 mg/dl (7.22 mmol/l), was present in 40% of patients at the time of admission. Hyperglycemia was an independent predictor of death at 30 days (RR 1.87) and at 1 year (RR 1.75) (both $P \leq 0.01$). Other outcomes that were significantly correlated with hyperglycemia, when compared with normal blood glucose, were length of stay (7 vs. 6 days, $P = 0.015$) and charges ($6,611 vs. $5,262, $P < 0.001$).

Recently, Parsons et al. (110) reported a study of magnetic resonance imaging (MRI) and MRS in acute stroke. Sixty-three acute stroke patients were prospectively evaluated with serial diffusion-weighted and perfusion-weighted MRI and acute blood glucose measurements. Median acute blood glucose was 133.2 mg/dl (7.4 mmol/l), range 104.4–172.8 mg/dl (5.8–9.6 mmol/l). A doubling of blood glucose from 90 to 180 mg/dl (5−10 mmol/l) led to a 60% reduction in penumbral salvage and a 56 cm^3 increase in final infarct size. For patients with acute perfusion-diffusion mismatch, acute hyperglycemia was correlated with reduced salvage of mismatch tissue from infarction, greater final infarct size, and worse functional outcome, independent of baseline stroke severity, lesion size, and diabetes status. Furthermore, higher acute blood glucose in patients with perfusion-diffusion mismatch was associated with greater acute-subacute lactate production, which, in turn, was independently associated with reduced salvage of mismatch tissue. Acute hyperglycemia increases brain lactate production and facilitates conversion of hypoperfused at-risk tissue into infarction, which may adversely affect stroke outcome.

These numerous observational studies further support the need for randomized controlled trials that aggressively target glucose control in acute stroke. To date, there is just one report of a treat-to-target intervention in stroke patients. The Glucose Insulin in Stroke Trial (GIST) examined the safety of GIK infusion in treating to a target glucose of 72–126 mg/dl (4–7 mmol/l). Lowering plasma glucose levels was found to be without significant risk of hypoglycemia or excess mortality in patients with acute stroke and mild-to-moderate hyperglycemia (206). No data on functional recovery were reported. While it is promising that these investigators were able to lower plasma glucose without increasing risk of hypoglycemia or mortality for stroke patients, until further studies test the effectiveness of this approach and possible impact on outcomes, it cannot be considered standard practice.

Hyperglycemia is associated with worsened outcomes in patients with acute stroke and head injury, as evidenced by the large number of observational studies in the literature. It seems likely that the hyperglycemia associated with these acute neurologic conditions results from the effects of stress and release of insulin counterregulatory hormones. The elevated blood glucose may well be a marker of the level of stress the patient is experiencing. The hyperglycemia can be marked in these patients. Studies are needed to assess the role of antihyperglycemic pharmacotherapy in these settings for possible impact on outcomes. Clinical trials to investigate the impact of targeted glycemic control on outcomes in patients with stress hyperglycemia and/or known diabetes and acute neurologic illness are needed.

Evidence for a blood glucose threshold in acute neurologic disorders. Observational studies suggest a correlation between blood glucose level, mortality, morbidity, and health outcomes in patients with stroke.

- Capes et al.'s (96) metaanalysis identified an admission blood glucose >110 mg/dl (6.1 mmol/l) for increased mortality for acute stroke.
- Studies by Pulsinelli, Jorgenson, and Weir et al. (202) identified an admission blood glucose >120 mg/dl (6.67 mmol/l), 108 mg/dl (6 mmol/l), and 144 mg/dl (8 mmol/l), respectively, for increased severity ad mortality for acute stroke.
- Williams et al. (205) reported a threshold admission blood glucose ≥130 mg/dl (7.2 mmol/l) for increased mortality, length of stay, and charges in acute stroke.
- Scott et al. (206) demonstrated acceptable hypoglycemia risk and no excess 4-week mortality with glucose-insulin infusion treatment targeted to blood glucose range of 72–126 mg/dl (4–7 mmol/l) in acute stroke.
- Parsons et al. (110) reported that a doubling of blood glucose from 90 to 180 mg/dl (5–10 mmol/l) was associated with 60% worsening of penumbral salvage and a 56-cm^3 increase in infarct size.

HOW ARE TARGET BLOOD GLUCOSE LEVELS BEST ACHIEVED IN THE HOSPITAL?

Role of oral diabetes agents

No large studies have investigated the potential roles of various oral agents on outcomes in hospitalized patients with diabetes. A number of observational studies have commented on the outcomes of patients treated as outpatients with diet alone, oral agents, or insulin. However, the results are variable and the methods cannot account for patient characteristics that would influence clinician selection of the various therapies in the hospital setting. Of the three primary categories of oral agents, secretagogues (sulfonylureas and meglitinides), biguanides, and thiazolidinediones, none have been systematically studied for inpatient use. However, all three groups have characteristics that could impact acute care.

Sulfonylureas

Concern about inpatient use of sulfonylureas centers on vascular effects (207,208). Over 30 years ago the report of the University Group Diabetes Program proposed increased cardiovascular events in patients treated with sulfonylureas (209). This report resulted in an ongoing labeling caution for sulfonylureas and heart disease, although the findings have been questioned and have had very limited influence on prescribing habits. Residual fears seemingly were allayed with the findings of the U.K. Prospective Diabetes Study (UKPDS) (210). This large prospective trial did not find any evidence of increased frequency of MI among individuals treated with sulfonylureas. Rather, the trend was in the direction of reduced events. However, questions remain. For instance, it is possible that control of hyperglycemia by any means reduces the frequency of vascular events to a greater extent than any effect sulfonylureas may have to increase vascular events. A variety of studies have served to fuel continued controversy.

Ischemic preconditioning appears to be an adaptive, protective mechanism serving to reduce ischemic injury in humans (211,212). Sulfonylureas inhibit ATP-sensitive potassium channels, resulting in cell membrane depolarization, elevation of intracellular calcium, and cellular response (213,214). This mechanism may inhibit ischemic preconditioning (215–217). Various methods evaluating cardiac ischemic preconditioning have been used to compare certain of the available sulfonylureas. For example, using isolated rabbit hearts, researchers found that glyburide but not glimepiride reversed the beneficial effects of ischemic preconditioning and diazoxide in reducing infarct size (218). Other studies using similar animal heart models or cell cultures have found differences among the sulfonylureas, usually showing glyburide to be potentially more harmful than other agents studied (219–222). A unique, double-blind, placebo-controlled study using acute balloon occlusion of high-grade coronary stenoses in humans looked at the relative effects of intravenously administered placebo, glimepiride, or glyburide (223). The researchers measured mean ST segment shifts and time to angina. The results again demonstrated suppression of the myocardial preconditioning by glyburide but not by glimepiride. In perfused animal heart models, both glimepiride and glyburide also appear to reduce baseline coronary blood flow at high doses (220,224).

Cardiac effects of sulfonylureas have also been compared with other classes of oral diabetes medications. In individuals with type 2 diabetes, investigators found that glyburide increased QT dispersion (225). This effect, proposed to reflect risk for arrhythmias, was measured after 2 months of therapy with glyburide or metformin. Glyburide also increased QTc, while metformin produced no negative effects. This study is in contradiction to the conclusions of a study using isolated rabbit hearts, where glyburide exerted an antiarrhythmic effect despite repeat evidence that it interfered with postischemic hyperemia (226). There have been few other comparisons of sulfonylureas and metformin with regard to direct cardiac effects. In a study of rat ventricular myocytes, hyperglycemia induced abnormalities of myocyte relaxation. These abnormalities were improved when myocytes were incubated with metformin, but glyburide had no beneficial effect (227). Finally, one experiment recently evaluated the relative functional cardiac effects of glyburide versus insulin (228). In this study of patients with type 2 diabetes, left ventricular function was measured by echocardiography after 12-week treatment periods with each agent, attaining similar metabolic control. Neither treatment influenced resting cardiac function. However, after receiving dipyridamole, glyburide-treated patients experienced decreased left ventricular ejection fraction and increased wall motion score index. Insulin treatment did not produce these deleterious effects on contractility.

Although these various findings using different research models raise questions about potential adverse cardiovascular effects of sulfonylureas in general and glyburide in particular, they do not necessarily extrapolate to clinical relevancy. A series of observational studies have attempted to add to our knowledge about whether any of the negative effects of sulfonylureas impact on vascular events, but they have yielded mixed results. For example, outcomes of direct balloon angioplasty after AMI were evaluated comparing 67 patients taking sulfonylureas with 118 patients on other diabetes therapies (229). Logistic regression found sulfonylurea use to be independently associated with increased hospital mortality. Others have reported similar trends in patients receiving angioplasty (230). A third observational study investigated 636 elderly patients with diabetes (mean age 80 years) and previous MI. The researchers looked for subsequent coronary events, including fatal and nonfatal MI or sudden coronary death (231). They found sulfonylurea therapy to be a predictor of new coronary events compared with insulin or to diet therapy (82 vs. 69 and 70%, respectively). Not enough metformin-treated patients were included to comment statistically on a comparison with sulfonylureas.

Conversely, other observational studies have failed to support a relationship between sulfonylurea use and vascular events. Klaman et al. (232) found no differences in mortality or creatinine kinase (CK) elevations after acute MI in 245 patients with type 2 diabetes when comparing those treated with insulin, those treated with oral agents, or those newly diagnosed. Others have reported a similar lack of association with MI outcomes and sulfonylureas (233–236). In one study, ventricular fibrillation was found to be less associated with sulfonylurea therapy than with gliclazide or insulin (234). Finally, in a related vascular consideration, there was no evidence of increased stroke mortality or severity in patients with type 2 diabetes treated with sulfonylureas versus other therapies (237).

None of the studies looking at sulfonylurea effects on vascular inpatient mortality have been prospective. Investigators have not made attempts to separate out duration of therapy or whether sulfonylureas were continued after presentation to the hospital. The one prospective study looking at treatment after admission for AMI indicated a benefit for insulin therapy over conventional therapy with sulfonylureas, but the improved outcomes were proposed to occur as a benefit of improved glucose control (238). No suggestion was made that sulfonylurea therapy had specific negative effects.

Despite a spectrum of data raising concern about potential adverse effects of sulfonylureas in the inpatient setting, where cardiac or cerebral ischemia is a frequent problem in an at-risk population, there are insufficient data to specifically recommend against the use of sulfonylureas in this setting. However,

sulfonylureas have other limitations in the inpatient setting. Their long action and predisposition to hypoglycemia in patients not consuming their normal nutrition serve as relative contraindications to routine use in the hospital for many patients (239). Sulfonylureas do not generally allow rapid dose adjustment to meet the changing inpatient needs. Sulfonylureas also vary in duration of action between individuals and likely vary in the frequency with which they induce hypoglycemia (240).

Metformin

Metformin represents a second agent that individuals are likely to be using as an outpatient, with potential for continuation as an inpatient. There is a suggestion from the UKPDS that metformin may have cardioprotective effects, although the study was not powered to allow for a comparison with sulfonylureas (241).

The major limitation to metformin use in the hospital is a number of specific contraindications to its use, many of which occur in the hospital. All of these contraindications relate to a potentially fatal complication of metformin therapy, lactic acidosis. The most common risk factors for lactic acidosis in metformin-treated patients are cardiac disease, including CHF, hypoperfusion, renal insufficiency, old age, and chronic pulmonary disease (242). In an outpatient setting, using slightly variable criteria, 22–54% of patients treated with metformin have absolute or relative contraindications to its use (242–245). One recent report noted that 27% of patients on metformin in the hospital had at least one contraindication to its use (246). In 41% of these cases, metformin was continued despite the contraindication. This study seemingly underestimates the usual frequency of contraindications since it identified no individuals with CHF, a risk factor that has been frequently noted in many of the outpatient studies. Not surprisingly, a recent review of hospital Medicare data found that 11.2% of patients with concomitant diagnoses of diabetes and CHF were discharged with a prescription of metformin (247).

Recent evidence continues to indicate lactic acidosis is a rare complication, despite the relative frequency of risk factors (248). However, in the hospital,where the risk for hypoxia, hypoperfusion, and renal insufficiency is much higher, it still seems prudent to avoid the use of metformin in most patients. In addition to the risk of lactic acidosis, metformin has added side effects of nausea, diarrhea, and decreased appetite, all of which may be problematic during acute illness in the hospital.

Thiazolidinediones

Although thiazolidinediones have very few acute adverse effects (249,250), they do increase intravascular volume, a particular problem in those predisposed to CHF and potentially a problem for patients with hemodynamic changes related to admission diagnoses (e.g., acute coronary ischemia) or interventions common in hospitalized patients. The same study of Medicare patient hospital data cited above (247) found that 16.1% of patients with diabetes and CHF received a prescription for a thiazolidinedione at the time of discharge. Twenty-four percent of patients with these combined diagnoses received either metformin or a thiazolidinedione, both drugs carrying contraindications in this setting.

Most recently it has been demonstrated that when exposed to high concentrations of rosiglitazone, a monolayer of pulmonary artery endothelial cells will exhibit significantly increased permeability to albumin (251). Although this is a preliminary in vitro study, it raises the possibility of thiazolidinediones causing a direct effect on capillary permeability. This process may be of greater significance in the inpatient setting. On the positive side, thiazoladinediones may have benefits in preventing restenosis of coronary arteries after placement of coronary stents in patients with type 2 diabetes (252). For inpatient glucose control, however, thiazolidinediones are not suitable for initiation in the hospital because the onset of effect, which is mediated through nuclear transcription, is quite slow.

In summary, each of the major classes of oral agents has significant limitations for inpatient use. Additionally, they provide little flexibility or opportunity for titration in a setting where acute changes demand these characteristics. Therefore, insulin, when used properly, may have many advantages in the hospital setting.

Use of insulin

As in the outpatient setting, in the hospital a thorough understanding of normal insulin physiology and the pharmacokinetics of exogenous insulin is essential for providing effective insulin therapy. The inpatient insulin regimen must be matched or tailored to the specific clinical circumstance of the individual patient.

Components of the insulin dose requirement defined physiologically. In the outpatient setting, it is convenient to think of the insulin dose requirement in physiologic terms as consisting of "basal" and "prandial" needs. In the hospital, nutritional intake is not necessarily provided as discrete meals. The insulin dose requirement may be thought of as consisting of "basal" and "nutritional" needs. The term "nutritional insulin requirement" refers to the amount of insulin necessary to cover intravenous dextrose, TPN, enteral feedings, nutritional supplements administered, or discrete meals. When patients eat discrete meals without receiving other nutritional supplementation, the nutritional insulin requirement is the same as the "prandial" requirement. The term "basal insulin requirement" is used to refer to the amount of exogenous insulin per unit of time necessary to prevent unchecked gluconeogenesis and ketogenesis.

An additional variable that determines total insulin needs in the hospital is an increase in insulin requirement that generally accompanies acute illness. Insulin resistance occurs due to counterregulatory hormone responses to stress (e.g., surgery) and/or illness and the use of corticosteroids, pressors, or other diabetogenic drugs. The net effect of these factors is an increase in insulin requirement, compared with a nonsick population. This proportion of insulin requirement specific to illness is referred to as "illness" or "stress-related" insulin and varies between individuals (Fig. 2).

Is the patient insulin deficient or non–insulin deficient? As in the outpatient setting, a key component to providing effective insulin therapy in the hospital setting is determining whether a patient has the ability to produce endogenous insulin. Patients who have a known history of type 1 diabetes are by definition insulin deficient (3). In addition, other clinical features may be helpful in determining the level of insulin deficiency (Table 2). Patients determined to be insulin deficient require basal insulin replacement to prevent iatrogenic diabetic ketoacidosis, i.e., they must be treated with insulin at all times.

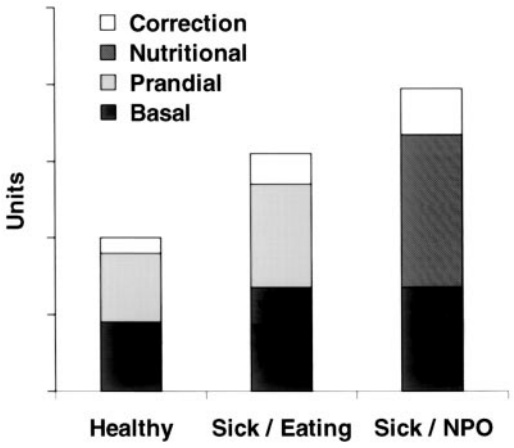

Figure 2—*Insulin requirements in health and illness. Components of insulin requirement are divided into basal, prandial or nutritional, and correction insulin. When writing insulin orders, the basal and prandial/nutritional insulin doses are written as programmed (scheduled) insulin, and correction-dose insulin is written as an algorithm to supplement the scheduled insulin (see online appendix 2). Programmed and correction insulin are increased to meet the higher daily basal and prandial or nutritional requirements. Total insulin requirements may vary widely.*

Subcutaneous insulin therapy. Subcutaneous insulin therapy may be used to attain glucose control in most hospitalized patients with diabetes. The components of the daily insulin dose requirement can be met by a variety of insulins, depending on the particular hospital situation. Subcutaneous insulin therapy is subdivided into programmed or scheduled insulin and supplemental or correction insulin (Table 3).

Scheduled insulin therapy. This review will use the term "programmed" or "scheduled insulin requirement" to refer to the dose requirement in the hospital necessary to cover the both basal and nutritional needs. For patients who are eating discrete meals, it is appropriate to consider the basal and prandial components of the insulin requirement separately.

Basal insulin therapy for patients who are eating. Subcutaneous basal insulin can be provided by any one of several strategies. These include continuous subcutaneous insulin infusion (CSII) or subcutaneous injection of intermediate-acting insulin (including premixed insulin) or of long-acting insulin analogs. Some of these methods result in peaks of insulin action that may exceed the basal needs of the patient, causing hypoglycemia. This is most likely to occur as the acute illness begins to resolve and basal insulin requirements that were elevated due to stress and/or illness begin to return to normal levels. Although selected in part for basal coverage, NPH, lente, and to some extent ultralente insulin also deliver peaks of insulin that potentially can cover prandial needs, albeit with variable capability for matching the timing of nutritional intake. When NPH insulin is used in very low doses, it can also be administered four times daily as an alternate way to provide basal insulin action (253).

Prandial insulin therapy for patients who are eating. Prandial insulin replacement has its main effect on peripheral glucose disposal into muscle. Also referred to as "bolus" or "mealtime" insulin, prandial insulin is usually administered before eating. There are occasional situations when this insulin may be injected immediately after eating, such as when it is unclear how much food will be eaten. In such situations, the quantity of carbohydrates taken can be counted and an appropriate amount of rapid-acting analog can be injected. The technique of "carbohydrate counting" may be useful for patients practicing insulin self-management. The rapid-acting insulin analogs, insulin lispro and aspart, are excellent prandial insulins. Regular insulin is more accurately considered to have both basal and prandial components due to its longer duration of action. Similarly, NPH and lente insulins, with their distinct peaks and prolonged action, can be used for both their basal and prandial insulin effects. For hospitalized patients with severe insulin deficiency, this can be a disadvantage since the timing of meals and the quantity of food is often inconsistent.

Basal insulin therapy for patients who are not eating. While not eating, patients who are not insulin deficient may not require basal insulin. Since reduction of caloric intake may alter insulin resistance substantially in type 2 diabetes, sometimes allowing previously insulin-requiring patients to be controlled with endogenous insulin production alone, the basal requirement is not easily determined. However, withholding basal insulin in insulin-deficient patients results in a rapid rise in blood glucose by 45 mg/dl (2.5 mmol/l) per hour until ketoacidosis occurs (rev. in 254). This situation can occur when "sliding scale" insulin therapy is the sole method of insulin coverage (255). Scheduled basal insulin therapy for patients who are not eating can be provided by a number of insulin types and methods.

Insulin for patients with intermittent nutritional intake. Hospitalized patients may receive nutrition intermittently, as with patients who are being transitioned between NPO status and regular diet, patients with anorexia or nausea, or patients receiving overnight cycling of enteral feedings. Appropriate insulins used in combination therapy might include regular, intermediate, and long-acting insulins or analogs, administered to cover basal needs and also timed to match the intermittent nutritional intake.

Illness-related or stress dose insulin therapy. The illness-related insulin can be apportioned between the basal insulin, the nutritional or prandial insulin, and the correction doses. It is important to point out that illness-related insulin requirements decrease as the patient's condition improves and, thus, in many situations may be difficult to precisely replace (Fig. 2). In attempting to meet the illness-related insulin requirement, and to later return to lower doses, it is important to recall that intravenous insulin infusion gives the greatest flexibility and that long-acting analog gives the least, with other preparations or routes being intermediate. Rapid changes in illness-related insulin requirements necessitate close blood glucose monitoring and daily

Table 2—*Clinical characteristics of the patient with insulin deficiency*

- Known type 1 diabetes
- History of pancreatectomy or pancreatic dysfunction
- History of wide fluctuations in blood glucose levels
- History diabetic ketoacidosis
- History of insulin use for >5 years and/or a history of diabetes for >10 years

Adapted from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (3) and consensus from the authors.

Table 3—*Practical guidelines for hospital use of insulin*

Clinical setting	Programmed/scheduled insulin option(s)		Supplemental/correction-insulin option(s)	Comments
	Basal	Prandial and/or nutritional		
				• Total daily insulin requirement may be calculated based on prior insulin doses or as 0.6 units · kg^{-1} · day^{-1} • Basal insulin generally accounts for 40–50% of daily insulin requirement • Prandial and/or nutritional or supplemental/correction doses may be calculated as 10–20% of total daily insulin requirement for each dose • Patients with type 1 diabetes always require continuous insulin coverage to avoid ketosis
Eating meals	• Int-I bid or hs • LA-I hs or am • Insulin drip	• Reg-I or rapid-I ac− B&D or B, L, and D	• Reg-I or rapid-I ac +/− hs	• Give Reg-I, 30–45 min ac; rapid-I, 0–15 min ac • Glargine given as once-daily dose, usually at hs • Avoid/minimize Reg-I and rapid-I doses at hs to decrease risk of nocturnal hypoglycemia • 70/30 or 75/25 insulin may be used ac breakfast and dinner to meet both basal and prandial needs • Insulin drip is Rx of choice in severely decompensated type 1, with or without DKA, and in type 2 with HHS
Not eating	• Insulin drip • Int-I bid or hs • LA-I hs or am	N/A	• Reg-I q 4–6 hours • Rapid-I q 4 hours	
Perioperative or periprocedural				
Will eat post-op or postprocedure (e.g., cataract extraction, cardiac catheterization, endoscopy)	Base on prior insulin Rx: • Int-I give 1/2-2/3 usual am dose • LA-I glargine, continue usual dose pm prior	When resumes eating • Restart prior doses of Reg-I or rapid-I ac	Until resumes eating: • Reg-I q 4–6 h • Rapid-I q 4 h	• Usual insulin and/or oral agent doses given the night prior to surgery to assure adequate glycemic control on the morning of the procedure • Patients with diabetes should be on the OR list for the early morning to minimize amount of time that they will be kept NPO. This decreases risk of hypoglycemia and allows maintenance of optimum metabolic homeostasis
Will not eat (e.g., major surgery)	• Insulin drip • Reg-I q 4–6 hours • rapid-I q 4 hours • Int-I, give ½ usual am dose • LA-I glargine, give usual daily dose	N/A	Until resumes eating: • Reg-I q 4–6 h • Rapid-I q 4 h	• Where a prolonged postoperative npo period is anticipated, e.g., cardiothoracic, major abdominal, CNS cases, insulin drip Rx is recommended • Starting dose for perioperative maintenance insulin drip is 0.2 units · kg^{-1} · h^{-1}
ICU	If npo and/or clinically unstable: • Insulin drip • Reg-I q 4–6 h • Rapid-I q 4 h If eating: • Continue prior Int-I or LA-I	If npo: • N/A If eating: • Reg-I or RA-I ac and hs	• Reg-I q 4–6 h • Rapid-I q 4 h	• Evidence-based outcomes studies support use of insulin drip as Rx of choice for decompensated diabetes in the ICU setting including coronary care (acute myocardial infarction) and surgical intensive care units (Malmberg, Van den Berghe, Furnary)
Enteral tube feeding				
Continuous	24 h: • Int-I bid; • LA-I hs or am Daytime only: • Int-I am	• Reg-I q 4–6 h • Rapid-I q 4 h During tube feeding delivery period only: • Reg-I q 4–6 h • Rapid-I q 4 h	• Reg-I q 4–6 hours • Rapid-I q 4 hours	• Basal insulin dose generally no more than 40% of total daily insulin requirement to avoid hypoglycemia if enteral feeding interrupted • Nutritional insulin requirements met with programmed doses of reg-I or rapid-I • May use low-dose int-I at hs to control fasting hyperglycemia • If tube feeding interrupted, e.g., for procedure or intolerance, increase frequency of fingerstick BG checks
Bolus	24 h: • Int-I bid; • LA-I hs or am	• Reg-I q 4–6 h • Rapid-I q 4 h	• Reg-I q 4–6 h • Rapid-I q 4 h	• Give reg-I, 30–45 mins, or rapid-I, 0–15 mins prior to bolus to control post-bolus BG excursions • Check finger stick BG 2 h after reg-I or 1 h after rapid-I to determine dose adjustments for post-bolus target BG < 180 mg/dl • May use low-dose int-I at hs to control fasting hyperglycemia

Bolus (cont.)	Daytime only: ● Int-I am	During bolus delivery period only: ● Reg-I q 4–6 h ● Rapid-I q 4 h	
TPN	● Reg-I added to TPN bags	● Reg-I q 4–6 h	● Basal and nutritional insulin needs met with reg-I added to TPN bag directly ● To determine daily dose of insulin to add to TPN bag, consider use of separate IV insulin infusion for 24 h to determine daily insulin requirement, then add 2/3 of this amount to subsequent TPN bags; or add 2/3 of total units of insulin administered SQ the previous day to the next day's TPN bag as reg-I, until daily dose determined ● Use SQ insulin with caution with TPN. Lack of correlation of insulin peaks and troughs with nutrient delivery may lead to erratic BG control
Transition to oral intake	● Int-I bid ● LA-I hs or am	● Reg-I or rapid-I ac	● Reg-I or rapid-I ac ac +/− hs ● Give reg-I, 30–45 min or rapid-I 0–15 min prior to meal to control postprandial BG excursions ● Postprandial target BG < 180 mg/dl ● Check fingerstick BG 2 h after reg-I or 1 h after rapid-I to determine prandial insulin dose adjustments
High-dose glucocorticoid Rx	● Insulin drip; Int-I bid; LA-I hs or am	Reg-I or RA-I: ●ac (B and D) or ac (B, L, and D) if eating; or q 4–6 h if NPO	Reg-I or rapid-I: ●ac and hs if eating; or q 4–6 hours if NPO ● High-dose glucocorticoids raise insulin requirements ● Adjust/increase insulin doses to counter postprandial hyperglycemia and BG peak that may occur 8–12 h following once-daily GC dose ● Alternate-day steroid doses require alternate-day insulin doses

ac, before meals; am, morning; B, breakfast; BG, blood glucose; D, dinner; DKA, diabetic ketoacidosis; GC, glucocorticoid; HHS, hyperglycemic hyperosmolar state; hs, bedtime; I, insulin; Int-I, intermediate acting insulin (NPH or Lente); IV, intravenous; L, lunch; LA-I, long-acting insulin (glargine or ultralente); OR, operating room; q, every; qd, every day; rapid-I, rapid acting insulin (lispro or aspart); Reg-I, regular insulin; SQ, subcutaneous.

changes in the scheduled insulin doses, as the blood glucose levels dictate.

Correction-dose insulin therapy. Also called "supplemental" insulin, this usually refers to the insulin used to treat hyperglycemia that occurs before meals or between meals. At bedtime, correction-dose insulin is often administered in a reduced dose compared with other times of the day in order to avoid nocturnal hypoglycemia. Correction-dose insulin may also refer to insulin used to correct hyperglycemia in the NPO patient or in the patient who is receiving scheduled nutritional and basal insulin but not eating discrete meals. Correction-dose insulin should not be confused with "sliding scale insulin," which usually refers to a set amount of insulin administered for hyperglycemia without regard to the timing of the food, the presence or absence of preexisting insulin administration, or even individualization of the patient's sensitivity to insulin.

The traditional sliding scale insulin regimens, usually consisting of regular insulin without any intermediate or long-acting insulins, have been shown to be ineffective at best and dangerous at worst (255–257). Problems cited with sliding scale insulin regimens are that the sliding scale regimen prescribed on admission is likely to be used throughout the hospital stay without modification (255). Second, sliding scale insulin therapy treats hyperglycemia after it has already occurred, instead of preventing the occurrence of hyperglycemia. This "reactive" approach can lead to rapid changes in blood glucose levels, exacerbating both hyperglycemia and hypoglycemia.

Correction-dose insulin therapy is an important adjunct to scheduled insulin, both as a dose-finding strategy and as a supplement when rapid changes in insulin requirements lead to hyperglycemia. If correction doses are frequently required, it is recommended that the scheduled insulin doses be increased the following day to accommodate the increased insulin needs.

Writing insulin orders. An example of an insulin order form that prompts the physician to address all three components of insulin therapy (i.e., basal, prandial, and correction dose) is provided (see online appendix 1 [available at http://care.diabetesjournals.org]). The forms can be incorporated into computerized order sets and other prompting methods

Table 4—*Indication for intravenous insulin infusion among nonpregnant adults with established diabetes or hyperglycemia*

Indication	Strength of Evidence
Diabetic ketoacidosis and nonketotic hyperosmolar state	A
General preoperative, intraoperative, and postoperative care	C
Postoperative period following heart surgery	B
Organ transplantation	E
MI or cardiogenic shock	A
Stroke	E
Exacerbated hyperglycemia during high-dose glucocorticoid therapy	E
NPO status in type 1 diabetes	E
Critically ill surgical patient requiring mechanical ventilation	A
Dose-finding strategy, anticipatory to initiation or reinitiating of subcutaneous insulin therapy in type 1 or type 2 diabetes	C

to reduce errors. Practice guidelines for using insulin under various clinical circumstances are summarized in Table 3.

Intravenous insulin infusion. The only method of insulin delivery specifically developed for use in the hospital is continuous intravenous infusion, using regular crystalline insulin. There is no advantage to using insulin lispro or aspart in an intravenous insulin infusion. The medical literature supports the use of intravenous insulin infusion in preference to the subcutaneous route of insulin administration for several clinical indications among nonpregnant adults, including diabetic ketoacidosis and nonketotic hyperosmolar state (258–275); general preoperative, intraoperative, and postoperative care (257,276–290); the postoperative period following heart surgery (142,196,198, 290,291); organ transplantation (297); or cardiogenic shock (128,194,292–296) and possibly stroke (147); exacerbated hyperglycemia during high-dose glucocorticoid therapy (297); NPO status (298); critical care illness (2,299–301); and as a dose-finding strategy, anticipatory to initiation or reinitiation of subcutaneous insulin therapy in type 1 or type 2 diabetes (Table 4) (302–304). Some of these settings may be characterized by, or associated with, severe or rapidly changing insulin requirements, generalized patient edema, impaired perfusion of subcutaneous sites, requirement for pressor support, and/or use of total parenteral nutrition. In these settings the intravenous route for insulin administration surpasses the subcutaneous route with respect to rapidity of onset of effect in controlling hyperglycemia, overall ability to achieve glycemic control, and most importantly, nonglycemic patient outcomes. During intravenous insulin infusion used to control hyperglycemic crises, hypoglycemia (if it occurs) is short-lived, whereas in the same clinical settings repeated administration of subcutaneous insulin may result in "stacking" of the insulin's effect, causing protracted hypoglycemia. As an alternative to continuous intravenous infusion, repeated intravenous bolus therapy also has been advocated for patients with type 2 diabetes during anesthesia (305).

Depending on the indication for intravenous insulin infusion, caregivers may establish different glycemic thresholds for initiation of intravenous insulin therapy. For patients not hyperglycemic initially, it is best to assign a blood glucose threshold for initiation of the insulin infusion that is below the upper limit of the target range glucose at which the infusion protocol aims. For patients with type 1 diabetes, uninterrupted intravenous insulin infusion perioperatively is an acceptable and often the preferred method of delivering basal insulin. For these patients, intravenous insulin infusion therapy should be started before the end of the anticipated timeframe of action of previously administered subcutaneous insulin, i.e., before hyperglycemia or ketosis can develop. For patients having elective surgery, hourly measurements of capillary blood glucose may be ordered, and the intravenous infusion of insulin may be initiated at a low hourly rate when rising blood glucose levels (>120 mg/dl, or 6.7 mmol/l) indicate waning of the effects of previously administered intermediate or long-acting insulin. The desirability of infusing dextrose simultaneously depends on the blood glucose concentration and the condition for which the insulin infusion is being used (275,288).

Mixing the insulin infusion. Depending on availability of infusion pumps that accurately deliver very low hourly volumes, intravenous insulin therapy is conducted with regular crystalline insulin in a solution of 1 unit per 1 ml normal saline. The concentrated infusion is piggybacked into a dedicated running intravenous line. Highly concentrated solutions may be reserved for patients requiring volume restriction; otherwise, solutions as dilute as 1 unit insulin per 10 ml normal saline may be used (306,307). When the more dilute solutions are used, at least 50 ml of the insulin-containing solution should be allowed to run through the tubing before use (308). It is prudent to prepare and label the solutions in a central institutional pharmacy, if possible using the same concentration for all adult patients.

The use of a "priming bolus" to initiate intravenous insulin infusion is controversial (265). The half-life of an intravenous insulin bolus is about 4–5 min (309), and, although tissue effects are somewhat delayed, by 45 min insulin blood levels return virtually to baseline. Because repeated intravenous bolus insulin therapy does not maintain adequate blood insulin levels or target tissue action of insulin, the initial priming bolus of intravenous insulin, if used, must be followed by maintenance insulin infusion therapy (310,311).

Insulin infusion initiation. Commonly, for unstressed normoglycemic adults of average BMI, insulin infusion is initiated at 1 unit/h but adjusted as needed to maintain normoglycemia (i.e., the perioperative setting). The assumption that ~50% of the ambulatory daily insulin dose is the basal requirement can also be used to estimate initial hourly requirements for a normoglycemic, unstressed patient previously treated with insulin (312). Alternatively, a weight-based insulin dose may be calculated using 0.02 units $\cdot$ kg^{-1} $\cdot$ h^{-1} as a starting rate. A lower initial insulin infusion rate may be used for patients with low body weight or renal or hepatic failure or if the infusion is started within the timeframe of action of previously administered subcutaneous insulin. A higher initiation rate

such as ≥2 units/h may be used when hyperglycemia is present, when preadmission insulin requirements are high, or if the patient has conditions predicting the presence of insulin resistance. Among hyperglycemic type 1 and type 2 diabetic patients who were otherwise well and receiving no concomitant intravenous dextrose, the prime determinants of the initial hourly intravenous insulin requirement are the initial plasma glucose and BMI. After attainment of normoglycemia, only the BMI correlates with the hourly insulin infusion requirement (313). It has been argued that the maximum biologic effect of insulin might be expected at infusion rates of 10 units/h or less. However, some patients benefit from higher infusion rates according to setting, and use of hourly insulin infusion rates as high as 50 units/h has been reported, particularly in the intensive care setting (2).

Assignment and adjustment of the intravenous insulin infusion rate is determined by the caregiver, based on knowledge of the condition of the patient, the blood glucose level, and the response to previous therapy. Blood glucose determinations should be performed hourly until stability of blood glucose level has been demonstrated for 6–8 h; then, the frequency of blood glucose testing can be reduced to every 2–3 h. To avoid unwanted excursions of blood glucose, especially when making corrective changes in the insulin infusion rate, the pharmacodynamics of intravenous insulin administration and delay of tissue responsiveness following attainment of a given blood level of insulin must be considered. If concomitant infusion of dextrose is used, caregivers must be alert to the effects of abrupt changes of dextrose infusion rate. Well-conducted insulin infusion therapy should demonstrate progressively smaller oscillations of the hourly insulin infusion rate and narrower excursions of blood glucose, as the caregiver discovers the hourly rate that will maintain normoglycemia for a given patient.

Many institutions use insulin infusion algorithms that can be implemented by nursing staff (2,189,194,197,200,280, 298,301,304,307,314). Algorithms should incorporate the concept that maintenance requirements differ between patients and change over the course of treatment. The algorithm should facilitate communication between physicians and nurses, achieve correction of hyperglycemia in a timely manner, provide a method to determine the insulin infusion rate required to maintain blood sugars within a defined the target range, include a rule for making temporary corrective increments or decrements of insulin infusion rate without under- or overcompensation, and allow for adjustment of the maintenance rate as patient insulin sensitivity or carbohydrate intake changes. The algorithm should also contain directions as to how to proceed if hypoglycemia or a rapid fall in blood glucose occurs, as well as instructions as to how to transition the patient to scheduled subcutaneous insulin.

Physician orders to "titrate drip" to a given target blood glucose range, or protocols requiring application of mathematical rules by nursing staff, may be difficult to implement. A mathematical algorithm can be reduced to tabular form, in which each column indicates different insulin infusion rates necessary to maintain target range control and shows appropriate infusions rates necessary for correction at given blood glucose levels, accompanied by a rule for shifting between columns (see online appendix 2 [available at http://care.diabetesjournals.org]) (314). It is prudent to provide inservice teaching of pharmacy, nursing, and physician staff on the use of insulin drip protocols (307).

Transition from intravenous to subcutaneous insulin therapy. To maintain effective blood levels of insulin, it is necessary to administer short- or rapid-acting insulin subcutaneously 1–2 h before discontinuation of the intravenous insulin infusion (191,199,315–319). An intermediate or long-acting insulin must be injected 2–3 h before discontinuing the insulin infusion. In transitioning from intravenous insulin infusion to subcutaneous therapy, the caregiver may order subcutaneous insulin with appropriate duration of action to be administered as a single dose or repeatedly to maintain basal effect until the time of day when the choice of insulin or analog preferred for basal effect normally would be provided. For example, a patient who normally uses glargine at bedtime and lispro before meals, and whose insulin infusion will be stopped at lunchtime, could receive a dose of lispro and a one-time injection of NPH before interruption of the insulin infusion.

Initial scheduled insulin, dose decisions, and correction-dose calculations. The initial doses of scheduled subcutaneous insulin are based on previously established dose requirements, previous experience for the same patient during similar circumstances of nutritional change or drug administration, requirements during continuous insulin infusion (if stable), knowledge of stability or instability of medical condition and nutritional intake, assessment of medical stress, and/or body weight. Correction doses for various ranges of total daily insulin requirement or body weight can be expressed in tabular form, as a component of standardized inpatient orders (see online appendix 1). For most insulin-sensitive patients, 1 unit of rapid-acting insulin will lower blood glucose by 50–100 mg/dl (2.8–5.6 mmol) (320). A reduction of the correction dose at bedtime is appropriate to reduce the risk of nocturnal hypoglycemia. For patients whose insulin requirements are unknown and whose nutritional intake will be adequate, an assumption concerning requirement for scheduled insulin based on body weight would be about 0.5–0.7 units/kg insulin per 24-h period for patients having type 1 diabetes and 0.4–1.0 units/kg or more for patients having type 2 diabetes, starting low and working up to the dose to meet demonstrated needs, with assignment of a corresponding scale for correction doses. If nutritional intake is severely curtailed, for type 1 diabetes the amount of scheduled insulin calculated by body weight should be reduced by 50%. For type 2 diabetes, a safe initial assumption in the absence of nutritional intake would be that endogenous insulin might meet needs, requiring supplementation only with correction doses, until results of monitoring indicate the further need for scheduled insulin.

Perioperative insulin requirements. In the perioperative period for all type 1 diabetic patients and for those type 2 diabetic patients with demonstrated insulin deficiency, scheduled insulin intended to provide basal coverage should be administered on the night before surgery to assure optimum fasting blood glucose for the operative room. If insulin intended to meet basal needs is normally administered in the morning, in the case of type 1 diabetes the morning basal insulin is given without dose adjustment, and in the case of type 2 diabetes 50–100% of the basal insulin is administered on the morning of surgery. Correction doses may be

applied on the morning of surgery if the morning glucose concentration exceeds 180 mg/dl.

Appropriate use of insulin self-management. Recognition of the patient rights, patient responsibilities, and the importance of patient-oriented care are critical to the care of diabetes (321–323). In the ambulatory setting, patient self-management has a favorable impact on glycemic control and quality of life (324,325). Using the tools of multiple daily injections of insulin or CSII, patient self-management has been shown to be capable of improving glycemic control and microvascular outcomes (326–328). In multiple-dose insulin therapy, mealtime treatment with rapid-acting insulin analog improves hypoglycemia and postprandial hyperglycemia in comparison with conventional therapy in both type 2 (329) and type 1 diabetes (253,330–332). In comparison with conventional management using intermediate-acting insulin for basal effect, patients using long-acting insulin analog for basal insulin effect experience less overall or nocturnal hypoglycemia (333–336), better control of fasting plasma glucose levels (333,337), and lower HbA_{1c} levels (333). In CSII therapy, rapid-acting analogs improve control for most patients (338–340). Use of advanced carbohydrate counting and an insulin-to-carbohydrate ratio have markedly enhanced the success of patients to implement intensive self-management (341). Patients familiar with their own needs sometimes have experienced adverse events or, perceiving threat of adverse events, express frustration with rigidity of hospital routine and delegation of decision making to providers who are less likely to understand their immediate needs.

Self-management in the hospital may be appropriate for competent adult patients who have stable level of consciousness and reasonably stable known daily insulin requirements and successfully conduct self-management of diabetes at home, have physical skills appropriate to successfully self-administer insulin, perform self-monitoring of blood glucose, and have adequate oral intake. Appropriate patients are those already proficient in carbohydrate counting, use of multiple daily injections of insulin or insulin pump therapy, and sick-day management. The patient and physician in consultation with nursing staff must agree that patient self-management is appropriate under the conditions of hospitalization. Components of the program can include a physician order for self-management with respect to selection of food from a general diet, self-monitoring of blood glucose, self-determination and administration of insulin dose, and ranges of insulin to be taken. Patient record-keeping, sharing of results with nursing staff, and charting by nursing staff of self-determined glucose results and insulin administration should occur. If a subcutaneous insulin pump is used, provisions for assistance in troubleshooting pump problems need to be in place. Assistance might be required if equipment familiar to the patient is unavailable, if refrigeration is required, or if physical autonomy is imperfect. For example, decision making about dosage may be intact, but manual dexterity or availability of easily reached injection sites may be altered by the conditions of hospitalization. Additionally, help may be required in a situation of increasing insulin resistance or period of NPO where the patient may not know how to adjust his or her insulin doses appropriately.

Although the program should be developed in compliance with institutional and external regulatory requirements, consideration should be given to permitting self-use of equipment and drugs already in the possession of the patient but not normally on formulary. The program should not create additional burdens for dietary or nursing staff. As one of the likely barriers to implementation, institutions should recognize that fear of not only causing patient harm, but also of exposure of deficiencies of knowledge and skill, may underlie staff resistance to patient self-management programs. Staff may be trained in advance to understand that proficiency in making intensive management decisions or using specialized equipment is not expected of them by either their employer or the patient. Orders to replace self-management with provider-directed care should be written when changing the condition of the patient makes self-management inappropriate (342). Table 5 summarizes the components necessary for diabetes self-management.

Table 5—*Components for safe diabetes self-management in the hospital*

- Perform simultaneous laboratory-measured capillary or venous blood test and patient-performed capillary blood glucose test. The capillary blood glucose test should be ±15% of the laboratory test.
- Demonstration that the patient can self-administer insulin accurately.
- Patient is alert and is able to make appropriate decisions on insulin dose.
- All insulin administered by the patient and nurse is recorded in the medication record.
- Physician writes order that the patient may perform insulin self-management.

Preventing hypoglycemia

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the glycemic management of type 1 and type 2 diabetes (343–347). In the hospital, multiple additional risk factors for hypoglycemia are present, even among patients who are neither "brittle" nor tightly controlled. Patients who do not have diabetes may experience hypoglycemia in the hospital, in association with factors such as altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis (348). Patients having diabetes may develop hypoglycemia in association with the same conditions (349). Additional triggering events leading to iatrogenic hypoglycemia include sudden reduction of corticosteroid dose; altered ability of the patient to self-report symptoms; reduction of oral intake; emesis; new NPO status; reduction of rate of administration of intravenous dextrose; and unexpected interruption of enteral feedings or parenteral nutrition. Under-prescribing needed maintenance antihyperglycemic therapy is not always fully protective against such causes of hypoglycemia. Nevertheless, fear of hypoglycemia may contribute to inadequate prescribing of scheduled diabetes therapy or inappropriate reliance upon "sliding scale" monotherapy (255,256,350).

Despite the preventable nature of many inpatient episodes of hypoglycemia, institutions are more likely to have nursing protocols for treatment of hypoglycemia than for its prevention (351–359). Nursing and pharmacy staff must remain alert to the effects of antihyperglycemic therapy that may have been administered on a previous shift. Various conditions creating a high risk for hypoglycemia are listed in Table 6. If identified,

Table 6—*Conditions creating high risk for hypoglycemia in patients receiving scheduled (programmed) insulin*

- Sudden NPO status or reduction in oral intake
- Enteral feeding discontinued
- TPN or intravenous dextrose discontinued
- Premeal insulin given and meal not ingested
- Unexpected transport from nursing unit after rapid-action insulin given
- Reduction in corticosteroid dose

preventive strategies could potentially include a provision, under protocol or by physician order, to perform blood glucose testing more frequently and, for falling levels, to take preventive action.

Special situations: TPN

Hyperglycemia in patients without diabetes from TPN is based on a variety of factors—age (360), severity of illness (361), and the rate of dextrose infusion (362)—all of which affect the degree of hyperglycemia. In individuals with preexisting type 2 diabetes not previously receiving insulin therapy, 77% of patients required insulin to control glycemia during TPN (363). Insulin doses in this group averaged 100 ± 8 units/day.

There are no controlled trials examining which strategies are best for this situation. Adding incremental doses of insulin to the TPN is one option, but this may require days to determine the correct insulin dose (306). The use of a separate intravenous insulin infusion brings most patients within target within 24 h (364). Two-thirds to 100% of the total number of units of insulin used in the variable rate infusion over the previous 24-h period can subsequently be added to the subsequent TPN bag(s) (306,365).

Special situations: glucocorticoid therapy

Glucocorticoids are well known to affect carbohydrate metabolism. They increase hepatic glucose production, inhibit glucose uptake into muscle, and have a complex effect on β-cell function (366–368). The decrease in glucose uptake with glucocorticoids seems to be the major early defect (369,370), and thus it is not surprising that for hospitalized patients with well-controlled type 2 diabetes, postprandial hyperglycemia is the most significant problem. Although in some patients the hyperglycemia, if present, may be mild, in others the glucocorticoids may be responsible for hyperosmolar hyperglycemic syndrome (371). The best predictors of glucocorticoid-induced diabetes are family history of diabetes, increasing age, and glucocorticoid dose.

There are few studies examining how to best treat glucocorticoid-induced hyperglycemia. Thiazolidinediones may be effective for long-term treatment with glucocorticoids (372), but no insulin sensitizer would be appropriate for the initial management of acute hyperglycemia in the hospital due to the fact their antihyperglycemic effects will take weeks to occur. There is also an uncontrolled report suggesting that chromium may be beneficial for this population (373). Insulin is recommended as the drug of choice for the treatment of glucocorticoid-induced hyperglycemia. Although data are not available, due to the effect of glucocorticoids on postprandial glucose, an emphasis on the use of prandial insulin would be expected to have the best results. For patients receiving high-dose intravenous glucocorticoids, an intravenous insulin infusion may be appropriate (306). The insulin dose requirements are extremely difficult to predict, but with the insulin infusion it is possible to quickly reach the required insulin dosing. Furthermore, for short glucocorticoid boluses of no more than 2 or 3 days, the insulin infusion allows appropriate tapering of insulin infusion rates so that glycemic control is not compromised and hypoglycemic risks can be minimized as steroid doses are reduced. It should be emphasized that if intravenous insulin is not used, there will be a greater increase in prandial compared with basal insulin doses. There are no trials comparing the use of insulin lispro or insulin aspart to regular insulin for this situation.

Special situations: enteral feeding

Current enteral nutrition formulas are generally high in carbohydrate (with an emphasis on low–molecular weight carbohydrates) and low in fat and dietary fiber. Carbohydrates contribute 45–92% of calories (374). There are a variety of different protein sources in these enteral feedings, and there are no contraindications for use of any of these in people with diabetes. Generally, enteral formulas contain 7–16% of total calories from protein. For most institutionalized patients, it is recommended that protein intake should be 1.2–1.5 $g \cdot kg^{-1} \cdot day^{-1}$ (375). Most currently available standard formulas contain 25–40% of total calories from fat. There is current controversy as to how much of this fat source should be from n-3 compared with n-6 fatty acids. Not surprisingly, products that are lower in carbohydrate and higher in dietary fiber and fat have less of an impact on diabetes control (376,377).

There is only one study reporting glycemic outcomes for people with type 2 diabetes receiving different enteral formulas (378). Thirty-four patients were randomized to a reduced-carbohydrate, modified fat enteral formula or a standard high-carbohydrate feeding. After 3 months, HbA_{1c} levels were lower for the group receiving the reduced-carbohydrate formula, but this did not reach statistical significance. For those randomized to the high-carbohydrate formula, HDL cholesterol levels were lower and triglyceride concentrations were higher. Interestingly, in this small study, the group receiving the reduced-carbohydrate formula had 10% fewer infections.

There are no clinical trial data examining different strategies of insulin replacement for this population. For intermittent enteral feedings such as nocturnal tube feeding, NPH insulin, usually with a small dose of regular insulin, works well. The NPH insulin provides basal insulin coverage, while the regular insulin is administered before each tube feeding to control postprandial glucose levels. Doses should be calculated based on capillary glucose testing before and 2 h after each enteral feeding period. Continuous feeding may be managed by several different strategies; again, however, there are no data that have examined these management strategies. One could use once- or twice-daily insulin glargine. Ideally, one would start with a small basal dose and use correction-dose insulin as needed while the glargine dose is being increased. Alternatively, the initial dose could be estimated by the amount of insulin required from a 24-h intravenous insulin infusion. This, however, may not be an accurate assessment of actual subcutaneous insulin needs. The major concern about using insulin glargine or ultralente insulin for this population is that when the enteral feeding is discontinued, whether planned or not, the subcutaneous insulin depot

will result in a high risk of hypoglycemia, particularly if large doses of insulin are required. The use of NPH or regular insulin for this situation is also problematic since the peaks and troughs of insulin do not match the insulin requirements necessitated by the carbohydrate infusion. Although there is no ideal way to manage this problem, the safest appears to maintain target blood glucose at the high end of the target range using basal insulins. When the tube feeding is discontinued, either enteral or parenteral glucose must be infused until the subcutaneous insulin has dissipated.

HOW CAN SYSTEM DESIGN AND IMPLEMENTATION IMPROVE DIABETES CARE IN THE HOSPITAL?

— The design and implementation of protocols for maintaining glucose control in the hospital may provide useful guidance to the treating physician. Diabetes management may be offered effectively by primary care physicians or hospitalists, but involvement of appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes (314,379–381). For a variety of conditions, outcomes under standardized pathways or dose titration protocols are superior to those achieved by individualization of care (382). In evaluation of institutional performance, variability of treatment strategies among providers may itself be interpreted as a risk factor for unsafe practices, and "standardization to excellence" may be interpreted as a surrogate for patient safety (322,383). In the care of diabetes, implementation of standardized order sets for scheduled and correction-dose insulin may reduce reliance on sliding scale management (307). A team approach is needed to establish hospital pathways. To implement intravenous infusion of insulin for the majority of patients having prolonged NPO status, hospitals will need multidisciplinary support for using insulin infusion therapy outside of critical care units.

Patient safety, quality of care, variability of practice, and medical error have been the subjects of increasing national concern (384–390). Quality assessment programs that strive to promote a "culture of safety" commonly focus on diabetes. It has been reported that 11% of medication errors result from insulin misadministration (391), and insulin has been identified as one of several medications that deserve high alert status (392,393). Hypoglycemia may result from drug-dispensing errors, including mistaken administration of hypoglycemic agents to nondiabetic patients. For diabetic patients, frank prescribing errors, the use of trailing zeros after decimal points, or misinterpreted abbreviations for insulin may compromise patient safety (394–397). Because capital "U" can be mistaken for a numeral when handwritten, the word "units"should be spelled out in physician orders (391,398). The erroneous administration of a large dose of rapid-acting insulin in place of insulin glargine can easily occur, since insulin glargine and rapid-acting insulins look the same in the vial (both are clear). Barcoding of drugs and pharmacist participation in rounds and in surveillance of prescribing patterns may help reduce errors (399–404). Although some emphasis has been placed on institutional standardization of sliding scales (382,405), sliding scale monotherapy itself has been considered to be both ineffective compared with anticipatory management and frequently dangerous. A computerized order entry system can reduce utilization of sliding scale management (406). With present-day monitoring techniques, the inhouse development of ketoacidosis or hyperglycemic hyperosmolar state is generally preventable, and any occurrence should suggest the need for a root cause analysis (407–415). By tracking transfers or readmissions to the intensive care unit, it is sometimes possible to detect an opportunity for improvement, such as a recurrent pattern of failure to administer scheduled subcutaneous insulin at the termination of insulin infusion leading to development of metabolic emergency.

Both hypoglycemia and hyperglycemia are patient safety issues appropriate for continuous quality improvement (CQI) analysis. Nevertheless, as a focus for institutional CQI activities, hypoglycemia receives more attention, and hypoglycemic events are more readily defined and ascertained. Pharmacies can readily track for example the dispensing of D50 as an "antidote," administered by nursing staff without physician orders, or detect hypoglycemia through analysis of reports of adverse drug reactions (416). In contrast, although computer searches of the laboratory databank may be used to help identify instances of hyperglycemia, at many institutions point-of-care measurements will escape detection unless values are scanned into an electronic databank (417). Severe hyperglycemia (at least one glucose level >400–450 mg/dl), prolonged hyperglycemia (at least three consecutive glucose levels >250 mg/dl), and ketosis all can be used as quality-control indicators. The time from presentation to the emergency room with hyperglycemic emergency to the initiation of an insulin infusion may be viewed as a quality issue (268). The use of a balanced emphasis on both hypoglycemia and hyperglycemia by hospital quality-improvement programs has been linked to changes in practice patterns that result in improved control (418–420).

WHAT IS THE ROLE OF DIABETES SELF-MANAGEMENT EDUCATION FOR THE HOSPITALIZED PATIENT?

— Teaching diabetes self-management to patients in hospitals is a difficult and challenging task. Patients are hospitalized because they are ill, are under increased stress related to their hospitalization and diagnosis, and are in an environment that is not conducive to learning. In addition, patients are often unable to get the optimal amount of rest because of various distractions, such as the telephone, TV, personnel, meal times, testing, and procedures. The shock of diagnosis, denial, anger, grief, and many emotions frequently prevent or impair the person's ability to meaningfully participate in the educational process. Ideally, people with diabetes should be taught at a time and place conducive to learning: as an outpatient in a nationally recognized program of diabetes education classes.

For the hospitalized patient, diabetes "survival skills" education is generally considered a feasible approach. Patients are taught sufficient information to enable them to go home safely. Those newly diagnosed with diabetes or who are new to insulin and or blood glucose monitoring need to be instructed before discharge to help ensure safe care upon returning home. Those patients hospitalized because of a crisis related to diabetes management or poor care at home need education to hopefully prevent subsequent episodes of hospitalization. Goals of inpatient diabetes self-management education (DSME) are listed in Table 7.

Table 7—*Goals of inpatient DSME*

- Assess current knowledge and practices of diabetes self-management and how they impact patient's health status and reason for hospitalization
- Initiate diabetes education for patients newly diagnosed with diabetes
- Provide information on basic self-management skills to help ensure safe care postdischarge
- Team approach with other health professionals (e.g., physicians, nurses, dietitians, case managers, and social workers) coordinating care in the hospital and post discharge
- Provide information on community resources and diabetes education programs for continuing education
- The diabetes educator serves as a resource for nursing staff and other health care providers

The efficacy of hospital-based DSME on outcomes has not been tested in randomized prospective studies. Performing such a study that denies the basics of DSME to a control group is considered unethical (421). Given the limitations and ethics of study design, several studies suggest hospital-based DSME has substantial benefits in outcomes. Using historical controls, Muhlhauser et al. (422) reported a 66% reduction in hospitalization days and an 86% reduction in episodes of diabetic ketoacidosis after implementing an intensive inpatient-based education program for patients with type 1 diabetes. Four deaths occurred in the control group, compared with no deaths in the treatment group. All deaths were from acute diabetes-related complications.

Fedderson and Lockwood (423) conducted a prospective nonrandomized study at a single 713-bed teaching hospital. Within the hospital, four similar patient care units (PCUs) were identified for the study intervention. Two units were designated as the treatment units and two as the control units. For the control units, DSME was provided by the regular nursing staff. For the experimental units, a certified diabetes educator (CDE) was employed to provide education to both the staff nurses and directly to diabetic patients. The nurse CDE conducted three separate teaching sessions for the staff nurses in the experimental PCUs on information that an insulin-requiring patient with diabetes needs before discharge. The nurse CDE also provided direct patient education. The authors reported a mean reduction in hospital length of stay of 1.3 days in the experimental group versus the control group ($P < 0.005$).

Wood (424) compared the efficacy of individualized DSME (control group) to individualized DSME supplemented by 2-h group classes held weekly (experimental group). Patients medically unstable were excluded from the study. Based on a follow-up questionnaire, the experimental group reported better adherence for all self-care behaviors than the control group. Four months postdischarge, the experimental group had significantly fewer emergency room visits compared with the control group (2 vs. 20 visits, respectively, $P = 0.005$).

Writing DSME consult requests

When writing a request for consultation for diabetes education, the referral should state the specific reason for the referral (not just state "Diabetes Education"), any pertinent details regarding the patient status, the discharge plan and person referring for consult, and how to contact them (Table 8). Early referral is encouraged, especially for those patients newly diagnosed with diabetes. Patients should be medically stable and able to participate in the educational process. Patients who are in pain or sedated should not be referred for DSME until their medical condition improves. Including various disciplines in the plan of care is equally important. If caregivers are involved, it is important that they be identified and included in the teaching process. Patients who are cognitively impaired are not good candidates for teaching and should have alternative options of care considered. Topics to be covered should be relevant to the plan of care and ready to implement at the time of discharge.

It is best to maximize the time spent on topics immediately relevant to the patient's diabetes management. Registered dietitians should be consulted for medical nutritional therapy and patient teaching. Social workers and case managers should be involved with discharge planning and orders for home-health-nurse follow up upon discharge. Those likely in need of home health nursing referrals include newly diagnosed diabetic patients, patients new to insulin, the aged or infirm, and those for whom there are compliance concerns.

Patient assessment

Patient assessment assists with defining the patient's problems and acknowledging his or her concerns. When seeing an inpatient for an initial consultation, it is imperative to be able to focus on the greatest needs of the patient at that time. Knowing the reason for the consultation allows the educator to direct precious time and energy to those specific educational needs and to bring any necessary teaching materials/supplies to the bedside. Before actually seeing the patient, the diabetes educator should review the chart and, if necessary, speak with the referring physician or registered nurse who is caring for the patient in order to obtain additional information. Assessment critical to patient teaching includes:

- Knowledge, psychomotor skills, and affective domains
- Current level of self care
- Preferred learning styles
- Psychological status
- Stress factors that impair learning
- Social/cultural/religious beliefs
- Literacy skills
- Readiness to learn
- Assessment of abilities—age, mobility, visual acuity, hearing loss, and dexterity

Table 8—*Writing the DSME consult request*

Component of request	Example
Specific reason for consult and diagnosis	Diabetes education for insulin administration teaching for patient with new-onset type 2 diabetes
Discharge medication plan	Lantus 30 units hs, Novolog 6 units ac
Specific comments/instructions	Spanish-speaking patient; lives with daughter
Contact information	John Smith, MD, pager #

ac, before meals; hs, bedtime.

Characteristics of adult learners

In preparing to teach, it is good to keep in mind some of the characteristics of adult learners:

- Usually self-directed
- Must be receptive to learning
- Tend to be problem-focused rather than subject-oriented
- Inclusive of past experiences with diabetes
- Active participation

Deciding what to teach patients

Deciding what to teach patients in a limited timespan is determined mostly by medical necessity but also by the patient's previous experiences and desires. The patient must be psychologically and emotionally ready for teaching. Listening to concerns and acknowledging the patient's feelings without being judgmental is an important aspect of changing behavior. When patients are newly diagnosed with diabetes, teaching "survival skills" is the first step to outlining the principles of diabetes management. These may include:

- What is diabetes? Principles of treatment and prevention of complications
- Norms for blood glucose and target glucose levels for the individual
- Recognition, treatment, and prevention of hyperglycemia and hypoglycemia
- Medical nutrition therapy (instructed by a registered dietitian who, preferably, is a CDE)
- Medication
- Self-monitoring of blood glucose
- Insulin administration (if going home on insulin)
- Sick-day management
- Community resources
- Universal precautions for caregivers

Patients previously diagnosed with diabetes need to have specific needs identified, and their instruction must be targeted to those needs. Diabetes education in a hospital setting is not meant to provide comprehensive in-depth knowledge of diabetes management, but is intended to provide basic information for people to start a life-long process of continuing diabetes education.

Communication and discharge planning

Documentation, reviewing chart notes/suggestions, and oral communication are vital to coordinating care with successful outcomes for hospitalized patients with diabetes. Staff nurses need to work with patients on developing their skills and reinforcing knowledge of diabetes management. Medical orders and the discharge plan of care need to be appropriate, achievable, and agreeable to the patient and family. For effective discharge planning, collaboration among the treating physician, nurses, and the diabetes nurse educator is essential for providing continuity of care back to the outpatient setting. During discharge planning, the following questions should be addressed:

- Does the patient require outpatient DSME?
- Can the patient prepare his or her own meals?
- Can the patient perform self-monitoring of blood glucose at the prescribed frequency?
- Can the patient take his or her diabetes medications or insulin accurately?
- Is there a family member who can assist with tasks that the patient cannot perform?
- Is a visiting nurse needed to facilitate transition to the home?

Discharge diabetes medications

When arranging for hospital discharge, caution should be taken in prescribing antihyperglycemic therapy, especially for the elderly. A recent hospital discharge is a strong predictor of subsequent serious outpatient hypoglycemia (425). This observation should lead to caution in the planning of antihyperglycemic therapy at discharge and careful planning for follow-up. Prescribing patterns should take into consideration the evidence that among the sulfonylureas, glipizide is associated with less hypoglycemia than glyburide in the elderly (426).

WHAT IS THE ROLE OF MEDICAL NUTRITION THERAPY IN THE HOSPITALIZED PATIENT WITH DIABETES?

— Determining the nutritional needs of hospitalized patients with diabetes, writing a diet order to provide for those needs, and incorporating the current nutrition principles and recommendations for persons with diabetes can be a daunting task. Even though hospital diets are commonly ordered by calorie levels based on the "ADA diet," it has been recommended that the term "ADA diet" no longer be used (427). Since 1994, the ADA has not endorsed any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiologic parameters, and medication usage; these recommendations apply primarily to persons living in a home setting who, in conjunction with a team of health professionals, self-manage their diabetes.

The question is, then, how do you use medical nutrition therapy appropriately in the hospital? Nutrient needs often differ in the home versus the hospital setting. The diabetes treatment plan used in the hospital may differ from home, e.g., insulin may be used instead of oral medications. The types of food a person can eat may change, or the route of administration may differ, e.g., enteral or parenteral feedings may be used instead of solid foods. And lastly, the ability of institutions to individualize meal plans is greatly decreased. Because of the complexity of nutrition issues, it is recommended that a registered dietitian, knowledgeable and skilled in medical nutrition therapy, serve as the team member who provides medical nutrition therapy. The dietitian is responsible for integrating information about the patient's clinical condition, eating, and lifestyle habits and for establishing treatment goals in order to determine a realistic plan for nutrition therapy (428). Registered dietitians who specialize in nutrition support can play an invaluable role in the management of critically ill patients. However, it is essential that all members of the interdisciplinary team are knowledgeable of nutrition therapy.

Goals of medical nutrition therapy

For the hospitalized patient, the goals of nutrition therapy are multiple:

- Attain and maintain optimal metabolic control of blood glucose levels, lipid levels, and blood pressure to enhance recovery from illness and disease
- Incorporate nutrition therapies to treat the complications of diabetes, including hypertension, CVD, dyslipidemia, and nephropathy
- Provide adequate calories, as needs are often increased in illness and during recovery from surgery

- Improve health through use of nutritious foods
- Address individual needs based on personal, cultural, religious, and ethnic food preferences
- Provide a plan for continuing self-management education and follow-up care

Nutritional needs of hospitalized patients

The caloric needs of most hospitalized patients can be met through provision of 25–35 kcal/kg body wt (429,430). Protein needs vary on the basis of physiologic stress. Mildly stressed patients require 1.0 g/kg body wt; moderately to severely stressed patients may need 1.5 g/kg body wt. These levels are for patients with normal hepatic and renal function. The preferred route of feeding is the oral route. If intake is inadequate or if medical conditions prohibit oral feeding, then enteral of parenteral feedings will be needed.

Consistent carbohydrate diabetes meal-planning system

The consistent carbohydrate diabetes meal-planning system was developed to provide institutions with an up-to-date way of providing food service to patients in those settings. The system is not based on specific calorie levels, but rather on the amount of carbohydrate offered at each meal. This amount is consistent from meal to meal and day to day. Meals are based on heart-healthy diet principles—saturated fats and cholesterol are limited, and protein content falls within a usual diet's content of 15–20% of calories. Instead of focusing on the type of carbohydrate foods served, the emphasis is on the total amount of carbohydrate contained in the meal. The majority of carbohydrate foods should be whole grains, fruits, vegetables, and low-fat milk, but some sucrose-containing foods can be included as part of the total carbohydrate allowance (430). A typical day's menu provides ~1,500–2,000 calories, with a range of 12–15 carbohydrate servings (187–259 g) divided among meals and snacks.

Central to the rationale for this system is that the glycemic effect of carbohydrate relates more to the total amount of carbohydrate rather than the source. While a number of factors influence glycemic response to individual foods, ingestion of a variety of foods does not acutely alter glycemic response if the amount of carbohydrate is similar (430). Sucrose does not increase glycemia to a greater extent than isocaloric amounts of starch. The prandial (mealtime) insulin dose is based on the meal's carbohydrate content. Current recommendations for fat modification (430) are incorporated by basing the meals on a cardiac, heart-healthy menu when devising the consistent carbohydrate meal plan.

An advantage to the use of this system is that prandial insulin dosages can be ordered on the basis of the known carbohydrate content of the meal. For patients with a poor appetite and poor intake, the prandial insulin can be given after the meal based on the amount eaten. Using a consistent carbohydrate menu makes this easy to determine. Providing meals with this system eases the burden on the health care team of trying to individualize diets, especially when it is not practical, such as during a short hospital stay. Meals for patients with type 1 diabetes can easily be adjusted by altering the number of carbohydrate servings and snacks (428). Efficiencies in food service are realized and patient satisfaction is enhanced with this system (428,431). Another advantage is that the system reinforces carbohydrate counting meal planning taught to many persons with diabetes, particularly type 1 diabetic individuals using advanced carbohydrate counting. It serves as a basis for teaching newly diagnosed patients with diabetes about meal planning and can serve as a reference for home meals.

The meals served to patients with diabetes certainly affect glucose control, but it should be remembered it is not the only factor influencing glycemia. Hospitalized patients often have poor appetites and intake is suboptimal. Meals can be delayed or missed entirely due to tests and procedures. Other causes of poor glucose control include erratic absorption of insulin, counterregulatory hormone stress responses, increased insulin requirements, the length of time between premeal insulin and food consumption, and impaired gut motility caused by diabetic gastroparesis and medications, particularly narcotics (300).

How to order consistent carbohydrate diets

There is no single meal-planning system that meets the needs of all institutions. Budgetary issues, food-service employee time, local factors, and administration understanding and support affect the choice of a meal planning system (432). Many institutions are familiar with exchange diets and, therefore, some facilities still use them as a system for planning meals. Introduction of the consistent carbohydrate system requires a multidisciplinary effort, staff education, and patient education for the program to succeed, but it can offer clear benefits when implemented. Institutions can adapt the consistent carbohydrate system to meet their needs. A review of the implementation of the consistent carbohydrate system in institutions revealed some variations developed by various facilities (431), as described below.

One hospital terms the diet the "consistent carbohydrate diabetes diet." Calorie levels are not specified. Menus with food selections instruct patients to choose three to five carbohydrate foods at each meal, identifying the carbohydrate foods. Each contains 15 g carbohydrate. Dessert items with 30 g carbohydrate (two carbohydrate choices) or 15 g are included at lunch and dinner. Another facility uses the consistent carbohydrate menu with calorie ranges from low to very high. All carbohydrate-containing foods are grouped in one list on the menu. Other modifications of nutrients or textures can be added. Since no universal guideline exists for consistent carbohydrate diabetes diet ordering, it is encouraged that hospital nutrition committees specify their own ordering guidelines that meet the unique needs of their patients and capabilities of their nutrition staff.

Regardless of the type of meal planning system selected, the use of meal plans such as no concentrated sweets, no sugar added, low sugar, and liberal diabetic diets are no longer appropriate. These diets unnecessarily restrict sucrose and do not reflect the current evidence-based nutrition recommendations (433).

Special nutrition issues

Liquid diets. Sugar-free liquid diets are not appropriate for patients with diabetes. Calories and carbohydrates are needed to provide for normal physiologic processes. Patients given clear or full liquid diets should receive ~200 g carbohydrate, spread equally throughout the day in meals and snacks (428).

Surgery and progression diets. After surgery it is desirable to initiate feeding as soon as possible in order to protect intestinal integrity (428). Advancement from

clear liquid to full liquid to solid foods should be done as quickly as tolerated. Approximately 200 g carbohydrate should be provided daily in evenly divided doses at meals and snacks. During illness and surgery, glucose requirements increase. Hypoglycemia can occur without sufficient glucose (428).

Catabolic illness and nutrition support

During catabolic illness, nutritional needs are altered. Careful continuous monitoring of various nutrition parameters and glycemic status is essential so that nutritional needs are met and glycemic control is maintained. Catabolic illness can alter fluid balance and can lead to shrinkage of body fat and body cell mass, making nutrition assessment difficult. A recent weight loss of 10% indicates a need for thorough nutrition assessment. Moderate protein-calorie malnutrition can occur with an unintentional weight loss of 10–20%; if the loss is >20%, severe malnutrition is likely present (430). The time period over which the weight loss has occurred bears investigation, since a more rapid weight loss is more hazardous. The magnitude of recent weight loss with consideration of the presence of excess fluid often present in critically ill patients, the presence or absence of clinical markers of stress, and the amount of time the patient will be unable to eat should determine the need for nutrition intervention (429). A consultation to the registered dietitian is warranted in these cases.

Enteral feedings have several advantages over parenteral feedings, including lower costs, avoidance of catheter-related complications, the trophic effect on gastrointestinal cells, and the more physiologic route (429). While parenteral nutrition is necessary in certain situations, it is beneficial to progress to enteral tube feedings or oral intake as soon as possible. As with solid-food diets, the amount of carbohydrate present will have the greatest impact on blood glucose response (428). Medications, particularly insulin, can be adjusted to maintain glycemic control based on frequent blood glucose monitoring. The dietitian, in consultation with other members of the interdisciplinary team, determines the best method of feeding, the appropriate enteral formula, and the amounts of protein, lipid, and carbohydrate in parenteral formulations. It is important to not overfeed patients receiving nutrition support, as overfeeding can exacerbate hyperglycemia, cause abnormal liver function tests, and increase oxygen consumption and carbon dioxide production (429).

Nutrition guidelines for health care institutions

In 1997 the "Translation of the Diabetes Nutrition Recommendations for Health Care Institutions" technical review (428) and position statement (427) were published. The position statement has been republished without any substantive modifications (433). The original paper was based on the nutrition recommendations current at that time, but both the original and updated position statements conform to the current evidence-based nutrition recommendations (430).

Discharge planning

Patients with newly recognized diabetes require DSME during hospitalization and need detailed discharge planning for diabetes care. Discharge planning includes assessment of the patient's ability to pay for diabetes supplies and medications. Of patients with no prior history of diabetes who are found to have hyperglycemia (random blood glucose >125 mg/dl or 6.9 mmol/l) during hospitalization, 60% are likely to have diabetes at follow-up testing (8). For this reason, follow-up testing for diabetes based on ADA criteria (3) is recommended within 1 month of hospital discharge.

WHAT IS THE ROLE OF BEDSIDE GLUCOSE MONITORING IN THE HOSPITALIZED PATIENT?

Implementing intensive diabetes therapy in the hospital setting requires frequent and accurate blood glucose data. This measure is analogous to an additional "vital sign" for hospitalized patients with diabetes. Bedside glucose monitoring using capillary blood has advantages over laboratory venous glucose testing because the results can be obtained rapidly at the "point of care," where therapeutic decisions are made. For this reason, the terms bedside and point-of-care glucose monitoring are used interchangeably.

To date, no study has been conducted testing the effect of frequency of bedside glucose testing on the incidence of hyperglycemia or hypoglycemia in the hospital. Without such data, recommendations are based only on expert and consensus opinion. For patients who are eating, commonly recommended testing frequencies are premeal and at bedtime. For patients not eating, testing every 4–6 h is usually sufficient for determining correction insulin doses. Patients controlled with continuous intravenous insulin typically require hourly blood glucose testing until the blood glucose levels are stable, then every 2 h.

Bedside blood glucose testing is usually performed with portable glucose devices that are identical or similar to devices for home self-monitoring of blood glucose. Characteristics unique to the hospitalized patient and common to the nonhospitalized patient can lead to erroneous bedside blood glucose testing results (Table 9). Most of these errors can be prevented by implementing and maintaining a strong hospital quality-control program (434,435). The impact of specific interfering substances or hematocrit are device-specific (436–440). Elevated levels of multiple interfering substances may alter bedside glucose results, although each substance, by itself, may be below the interference threshold specified by the manufacturer (441).

New bedside glucose devices allow for identification of both patient and provider by reading a unique barcode. The glucose results can also be automatically downloaded into the hospital's central lab database, allowing for easier access and monitoring for quality-control purposes. Most currently used bedside glucose meters, though designed for capillary whole-blood testing, are calibrated to report results compatible to plasma, which allows for reliable comparison to the laboratory glucose test. For critically ill patients, hypotension, dehydration, anemia, and interfering substances in the blood may render capillary blood glucose testing inaccurate (437). Using arterial or venous blood with bedside glucose meters in these situations is likely more reliable, but frequent comparison with the laboratory glucose test is recommended to avoid errors in insulin therapy. Arterial concentrations are ~5 mg/dl (0.3 mmol) higher than capillary concentrations and ~10 mg/dl (0.5 mmol) higher than venous concentrations. In the study by Van den Berghe et al. (2), in which very strict glucose targets were maintained in critically ill patients, all glucose samples were performed with a

Table 9—*Conditions causing erroneous bedside blood glucose results*

Sources of analytical error	Sources of user error
Low hematocrit*	Inadequate meter calibration
High hematocrit†	Using a test strip that does not match the meter code or that has passed the expiration date
Shock and dehydration‡	Inadequate quality-control testing
Hypoxia‡	Poor meter maintenance
Hyperbilirubinemia, severe lipemia*	Poor technique in performing fingerprick
Specimen additives: sodium flouride†	Poor technique of applying drop of blood to the test strip
Drugs—acetaminophen overdose, ascorbic acid, dopamine, fluorescein, mannitol, salicylate‡	Failure to record results in patient's chart or to take action if blood glucose is out of target range

*Falsely elevates result; †falsely lowers result; ‡can either falsely lower or elevate result, depending on the device used.

glucose analyzer at 1- to 4-h intervals. The use of alternate-site glucose testing (i.e., arm, leg, or palm) in the hospital has not been studied. The use of alternate-site glucose testing may cause erroneous results when the blood glucose level is rapidly rising or falling and when hypoglycemia occurs (442).

As with any procedure handling blood, protective glove use is essential for health care personnel performing bedside glucose monitoring. The use of self-retracting lancet devices has the potential to eliminate the chance of needlestick injury and risk for infection. Table 10 outlines specific elements of a quality-control program deemed to be necessary for appropriate use of bedside blood glucose testing in the hospital (443). Key participants in the program are clinical laboratory representatives, nurses, physicians, and hospital administrators. Additional guidelines are published by the National Committee for Clinical Laboratory Standards (444). For patients practicing diabetes self-management in the hospital, a quality-control program to test the patient's blood glucose device and the patient's testing technique is necessary to ensure accurate results.

IS IMPROVED DIABETES CARE IN HOSPITALS COST EFFECTIVE?

— Of the $91.8 billion spent annually in the U.S. for direct medical expenditures for diabetes, hospital care accounts for the single largest component of expenditures, comprising $40 billion, or 43.9%, of the total cost (445). After adjustment for age, sex, and race/ethnicity, annual per capita costs for hospital care is $6,309 for persons with diabetes versus $2,971 for persons without diabetes—a cost ratio of 2.1. Similar increased hospital-related cost for diabetic patients is reported in Europe (446). This increased cost for hospital care is due to increased frequency of hospital admissions (447), increased length of stay, and increased cost per hospital day due to higher utilization of intensive care and procedures (448).

Furnary and colleagues (196,290) performed a cost-effectiveness analysis following implementation of a continuous intravenous insulin infusion program for the first 3 days after cardiac surgical procedures in diabetic patients. Compared with historical control subjects, the incidence of deep sternal wound infections (DSWIs) was reduced from 1.9 to 0.8%, and mortality from DSWIs reduced decreased from 19 to 3.8% after implementation of the protocol. The average excess length of stay from DSWI was 16 days, generating an average $26,400 in additional hospital charges. Furnary et al. (449) estimated the additional expense of insulin infusion at $125–150 per patient. Of 1,499 patients in the intervention group, the number of DWSIs prevented was 10, resulting in an average cost to prevent one DSWI at approximately $21,000. This estimate does not incorporate the potential effects of the intervention on other outcomes, such as a reduction in mortality, cost for chronic care, and lost income from work.

Van den Berghe et al. (2) reported a 34% reduction in hospital mortality in critically ill patients treated with intensive insulin therapy. Intensive insulin therapy reduced the duration of intensive care but not the overall length of stay in the hospital. Subsequent comparison of costs between the groups for rehabilitation, chronic care, home care, or loss of wages due to illness or mortality has not as yet been reported.

Levetan et al. (379) reported the impact of obtaining an endocrinology consultation, either alone or as part of multidisciplinary diabetes team (endocrinologist, diabetes nurse educator, and a registered dietitian), on hospital length of stay in patients admitted with the principal diagnosis of diabetes, including hyperosmolar state, diabetic ketoacidosis, and uncontrolled diabetes. In this nonrandomized observational study, the average length of stay of the diabetes team patients was 3.6 ± 1.7 days as compared with 8.2 ± 6.2 days for patients in the no-consultation group and 5.5 ± 3.4 days for the patients who received a traditional individual endocrine consultation. Possible reasons for shortened length of stay were more rapid normalization of glucose levels, more efficient transition from intravenous to subcutaneous insulin, faster transition to a definitive insulin or oral medication regimen, and more effective teaching of diabetes survival skills. Estimated cost savings from reduction in length of stay for the 34 patients seen by the diabetes team was $120,000 compared with the cost in salaries of $40,000.

In summary, the potential opportunity for cost savings from improved hospital outcomes, reduced mortality, and shortened length of stay for patients with diabetes and hospital-related hyperglycemia is substantial. Future studies using randomized prospective design are needed to verify these results.

SUGGESTIONS FOR FUTURE RESEARCH

— While outcomes studies that provide evidence for a clear role

Table 10—*Characteristics of an effective bedside glucose monitoring (BGM) quality-control program*

Characteristic
• A specifically designated responsible individual, preferably a laboratory professional, is involved in the administration and quality assurance of the BGM program.
• A written procedure for the BGM program.
• An organized training program that involves laboratory personnel and nursing staff.
• Defined frequencies and requirements for maintenance and cleaning of BGM instruments.
• Regular performance of quality control testing on each instrument (daily or by shift), depending on the frequency of patient testing.
• A policy to regularly compare the BGM results from each operator and instrument with results from a corresponding sample tested in the clinical laboratory. Suggest that all BGM results are, at least, within ±15% variation from the clinical laboratory results.
• Participation in an external proficiency testing program.
• Acknowledgment of the limitations of BGM and requirement of a clinical laboratory glucose determination when a BGM result is outside a defined range.
• Acknowledgment of the effect of hematocrit value variation on BGM results and establishment of hematocrit value limitations for the instrument in use.
• Determination of the bias of the instrument in use and communication of this information to the physicians and the institutional quality assurance program.

Adapted from Jones et al. (443).

Table 11—*Summary of major recommendations for hospital management of hyperglycemia*

Recommendation	Level of evidence
• Good metabolic control is associated with improved hospital outcomes. Target plasma glucose levels are: •<110 mg/dl preprandial and <180 mg/dl peak postprandial.	B
• Intensive insulin therapy with intravenous insulin, with the goal of maintaining blood glucose 80–110 mg/dl, reduces morbidity and mortality among critically ill patients in the surgical ICU.	A
• Intravenous insulin infusion is safe and effective for achieving metabolic control during major surgery, hemodynamic instability, and NPO status.	B
• Intravenous insulin infusion is safe and effective for patients who have poorly controlled diabetes and widely fluctuating blood glucose levels or who are insulin deficient or severely insulin resistant.	B
• Intravenous insulin infusion, followed by multidose subcutaneous insulin therapy, improves survival in diabetic patients after myocardial infarction.	A
• For insulin-deficient patients, despite reductions or the absence of caloric intake, basal insulin must be provided to prevent diabetic ketoacidosis.	B
• Use of scheduled insulin improves blood glucose control compared with orders based on sliding scale insulin coverage alone.	B
• For patients who are alert and demonstrate accurate insulin self-administration and glucose monitoring, insulin self-management should be allowed as an adjunct to standard nurse-delivered diabetes management.	E
• Patients with no prior history of diabetes who are found to have hyperglycemia (random blood glucose >125 mg/dl or 6.9 mmol/l) during hospitalization should have follow-up testing for diabetes within 1 month of hospital discharge.	E
• Establishing a multidisciplinary team that sets and implements institutional guidelines, protocols, and standardized order sets for the hospital results in reduced hypoglycemic and hyperglycemic events.	B
• Diabetes education, medical nutrition therapy, and timely diabetes-specific discharge planning are essential components of hospital-based diabetes care.	C

for targeted glucose control in the hospital management of diabetes are beginning to accumulate in the scientific literature, numerous questions related to how to best manage diabetes in this hospital setting remain to be addressed. These questions may be grouped into three main areas: health care outcomes attributable to glycemic control, specific strategies for insulin delivery, and processes for optimizing diabetes care and education in the hospital setting.

Health care outcomes related to glycemic control

Few studies in the literature contain randomized, controlled evidence to support specific interventions that target glucose control in various clinical settings. Work is clearly needed to provide rigorous evidence in the hospital management of diabetes in order to:

- Further define the role of targeted glucose control and the threshold for impact of blood glucose level on health care outcomes in diverse clinical settings, such as general medicine and surgery patients, and in specific circumstances, such as stroke, neurosurgery, and CVDs
- Examine clinical outcomes
- Examine health care economic outcomes such as length of stay and cost effectiveness
- Further examine the impact of specialist care and diabetes team management
- Define the impact of diabetes education.

Specific strategies for insulin delivery

Development and implementation of specific strategies for insulin delivery, based on knowledge of the pharmacokinetics of the currently available insulins, will allow physicians and nurses to overcome barriers to its effective use in managing blood glucose. Such strategies will need to demonstrate safety and efficacy of specific applications of insulin therapies that address known areas of need, including:

- Optimum methods for delivering basal insulin under various clinical conditions
- Feasibility of using subcutaneous glargine or detemir insulin to meet basal insulin requirements (e.g., for medicine services) in the operating

room and for periprocedural management
- The role of standardization of diabetes management and algorithmic care and validation of such pathways and tools
- Safety and practicality of delivering insulin infusion therapy outside the intensive care unit
- Simple algorithms for subcutaneous delivery of programmed basal, prandial/nutritional, and correction doses of insulin and insulin infusion algorithms.

Improved methods for glucose monitoring

Current methods for blood glucose monitoring are painful and time consuming. Improved methods for frequent and accurate blood glucose monitoring would enhance the ability to reach target blood glucose levels safely. Development of continuous glucose monitoring systems that are safe and accurate is encouraged.

Processes for optimizing diabetes care and education in the hospital setting

Because diabetes is seen in a broad spectrum of inpatients, processes need to be defined and tested to enable safe and effective patient management and optimization of outcomes. Areas of interest include:

- Strategies adopted by institutions to reduce errors, enhance safety, and improve quality of care
- Development and implementation of nursing policies effective for hypoglycemia prevention
- Impact of institutional hypoglycemia programs on willingness of physicians to prescribe insulin to adequately control hyperglycemia
- Whether correlation exists between institutional adherence to clinical pathways and algorithms and outcomes
- Most appropriate CQI measures for evaluation of performance in achieving glycemic control
- Most appropriate focus for regulatory organizations such as JCAHO.

CONCLUSIONS

— Hyperglycemia is associated with poor hospital outcomes. The key question for guiding therapy is whether hyperglycemia observed in the hospital is a simple marker for the underlying disease state (i.e., diabetes) or the severity of illness or if hyperglycemia itself, in conjunction with relative hypoinsulinemia, is pathogenic for tissue injury and poor hospital outcomes. Based on limited interventional studies in selected settings, aggressive control of blood glucose in the hospital may provide an opportunity to improve patient outcomes. Clinical trials are needed to answer these questions. The target blood glucose threshold to optimize outcomes in the hospital is not clearly defined but may be lower than previously thought. From a cost perspective, research and strategies targeting glucose control and diabetes care in the hospital have the potential to translate to substantial cost savings.

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