The prevalence of diabetes in the US population is substantial and growing. In 2005, according to data from the Centers for Disease Control and Prevention, the total occurrence of diabetes among people older than 20 years of age in the United States was estimated at 9.6% (20.6 million). For the age group of 60 years and older—the group most frequently hospitalized—the prevalence of diabetes was even higher, at 20.9% (10.3 million).

Hospitals have been affected by this surge in diabetes, with patient discharges of any listed diagnosis of diabetes more than doubling, from 2.2 million in 1980 to 5.1 million in 2003. Umpierrez and colleagues reported hyperglycemia in 38% of patients admitted to a community teaching hospital, including 26% who were known diabetics and 12% with no history of diabetes.

Outcomes Data
Contrary to previous clinical dogma that inpatient hyperglycemia is a natural response to physiologic stress and is not detrimental, the relationship of hyperglycemia in hospitalized patients and adverse patient outcomes is now well substantiated. Acute hyperglycemia in diabetics and nondiabetics has been shown in observational and interventional studies to adversely affect outcomes in patients with stroke, myocardial infarction, cardiac surgery, heart failure, and community-acquired pneumonia, as well as in surgical and medical intensive care unit (ICU) patients. Wound-healing rates and length of hospitalization stay are also adversely impacted by hyperglycemia.

A brief review of the literature reveals compelling evidence for hyperglycemia-induced harm. In postischemic stroke patients, a meta-analysis of the literature revealed that hyperglycemia is associated with a 3-fold increased risk of short-term mortality and poorer functional recovery. In addition, patients who were successfully recanalized with tissue plasminogen activator showed lower admission glucose levels (127 vs 146 mg/dL; P=0.039). In the setting of acute myocardial infarction, acute hyperglycemia on hospital admission, defined as greater than 10 mmol/L (180 mg/dL), was associated with impaired left ventricular function and a higher 30-day mortality after reperfusion therapy. In hospitalized patients with community-acquired pneumonia, McAllister and colleagues determined that an admission blood glucose greater than 11 mmol/L (>198 mg/dL) resulted in a 73% higher mortality risk and a 52% higher risk of in-hospital complications, compared to an admission level less than 6.1 mmol/L (110 mg/dL). In the prospective, observational Portland Diabetic Project, Furnary et al concluded that hyperglycemia during the first 3 postoperative days is independently predictive of mortality, deep sternal wound infection, and increased length of stay in diabetic cardiac surgery patients.

In 2 separate studies, van den Berghe and colleagues determined the effect of tight glycemic control on patient outcomes in surgical and medical ICUs. In mechanically ventilated, surgical ICU patients, dramatic
reductions in overall in-hospital mortality, bloodstream infections, acute renal failure, blood transfusions, and polyneuropathy were seen when blood glucose was 80 to 100 mg/dL, compared to 180 to 200 mg/dL.\textsuperscript{10} In medical ICU patients, strict glycemic control led to positive morbidity outcomes (accelerated ventilator weaning, prevention of new kidney injury, and decreased length of stay),\textsuperscript{16} albeit they were less substantial than in the surgical ICU study. Reduced mortality was also noted in the patients in the tight glycemic group who were in the medical ICU for more than 3 days.

**Mechanisms of Harm**

Normal homeostasis of multiple cellular functions is affected by hyperglycemia, including: 1) **immune function**—diminished, leukocyte adherence, phagocytosis, and chemotaxis\textsuperscript{17}; 2) **hemostasis**—increased platelet activation\textsuperscript{18-21}; increased fibrinogen, adhesion molecule over-expression, augmented C-reactive protein, and increased plasminogen activator inhibitor\textsuperscript{22}; 3) **vascular endothelial cell function**—reduced nitric oxide production\textsuperscript{21,23}; increased production of reactive oxygen intermediates\textsuperscript{22}; and disruption of the protective endothelial glycocalyx layer, resulting activation of coagulation\textsuperscript{24}, and 4) **inflammation**—increased release of proinflammatory mediators, including cytokines such as interleukin-6 and tumor necrosis factor \(\alpha\).\textsuperscript{25} These inflammatory mediators may promote acute thrombosis, sepsis, and heart failure, and are involved in the pathogenesis of atherosclerosis.\textsuperscript{26} Correction of elevated glucose levels is hypothesized to modify these adverse cellular effects. In addition, insulin administration itself may improve patient outcomes, because insulin can reduce cytokine and free fatty acid release, and normalize endothelium-dependent vasodilation via stimulation of nitric oxide synthesis.\textsuperscript{26,27}

**Recommended Glycemic Goals**

The American Diabetes Association (ADA) and the American College of Endocrinology (ACE) have released recommendations for blood glucose control in hospitalized patients (Table 1).\textsuperscript{28,29}

**Medication Management of Glycemic Control**

**INSULIN**

Insulin is the preferred drug therapy for inpatient management of hyperglycemia. In critically ill patients, the use of a continuous regular insulin infusion with frequent blood glucose monitoring allows for rapid adjustments in insulin dose to maintain tight glycemic control and, as noted previously, improved patient outcomes. Nurse-driven insulin infusion algorithms are employed by many institutions.\textsuperscript{26,30-32} For non-critically ill patients, use of basal-prandial-correction scale insulin therapy is recommended.\textsuperscript{28} A basal-prandial insulin regimen more closely mimics the normal physiologic pattern of insulin release and has been shown to provide more effective glycemic control in patients with type 2 diabetes compared with sliding-scale insulin alone.\textsuperscript{33} Basal insulin, administered in the form of once-daily glargine (Lantus, Aventis), once- or twice-daily detemir (Levemir, Novo Nordisk), or twice-daily isophane (Humulin N, Lilly; Novolin N, Novo Nordisk), provides glycemic control primarily during periods of fasting. Prandial insulin is administered as rapid-acting (aspart [Novolog, Novo Nordisk], glulisine [Apidra, Aventis], or lispro [Humalog, Lilly]) or short-acting insulin (regular [Humulin R, Lilly; Novolin R, Novo Nordisk]) and provides glycemic control of post-meal glucose excursions. Correction scale insulin is administered as rapid- or short-acting insulin before meals to “correct” elevated fasting blood glucose levels. A number of basal-prandial-correction scale protocols have been published.\textsuperscript{26,30-32,34} Most such protocols employ weight-based dosing with considerations for type 1 versus type 2 diabetes, dietary status, glucocorticoid therapy, parenteral and enteral nutrition, and other factors. Guidelines for transitioning patients from an I.V. insulin infusion to subcutaneous insulin injections have also been published.\textsuperscript{31,32,35,36} A detailed discussion of these insulin dosing formulas is beyond the scope of this article; The Society of Hospital Medicine Web site contains a “glycemic control resource room” with free access to insulin order sets and protocols from healthcare facilities across the country.\textsuperscript{37}

**SLIDING-SCALE INSULIN: AVOID AS MONOTHERAPY**

Use of sliding-scale insulin dosing alone is an ineffective therapy for managing hyperglycemia. Sliding-scale dosing is a “reactive” approach to managing elevated glucose levels. Insulin is administered only when the patient is hyperglycemic, and no basal insulin is provided. Also, sliding-scale dosing is typically not adjusted according to blood glucose readings during a patient’s hospital stay. The use of sliding-scale regular insulin can lead to “insulin stacking,” resulting in an increased risk of hypoglycemia.\textsuperscript{38-40} No clinical trials document patient benefit from sliding-scale insulin therapy,\textsuperscript{41} and current guidelines for inpatient hyperglycemia recommend against using it as monotherapy.\textsuperscript{29}

**NONINSULIN GLUCOSE-LOWERING AGENTS**

Noninsulin glucose-lowering agents are generally not recommended for inpatient glycemic management due to changing dynamics in patient clinical status. In

### Table 1. Goals for Blood Glucose Levels in Hospitalized Patients

<table>
<thead>
<tr>
<th></th>
<th>American Diabetes Association</th>
<th>American College of Endocrinology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive care unit</strong></td>
<td>As close to 110 mg/dL as possible and generally &lt;180 mg/dL</td>
<td>110 mg/dL</td>
</tr>
<tr>
<td><strong>Non-critical care units</strong></td>
<td>Pre-meal 90-130 mg/dL; postprandial &lt;180 mg/dL</td>
<td>Pre-meal 110 mg/dL; maximal glucose 180 mg/dL</td>
</tr>
</tbody>
</table>

Based on references 28 and 29.
situations of low carbohydrate intake, sulfonylureas and meglitinitides may increase the risk of hypoglycemia. Metformin is contraindicated in patients with renal impairment, liver disease, and pharmacologically treated heart failure, and within 48 hours of administration of I.V. contrast dye. Thiazolidinediones have a slow onset of action and may cause fluid retention, potentially exacerbating patient conditions such as decompensated heart failure; α-glucosidase inhibitors (acarbose [Precose, Bayer]; miglitol [Glyset, Pfizer]), as well as the incretin-mimetic exenatide (Byetta, Amylin), and the amylin-mimetic pramlintide (Symlin, Amylin) primarily reduce postprandial glucose elevations, and thus have a limited role in hospitalized patients with inconsistent dietary intake.

Barriers to Improved Glycemic Control

Even with evidence mounting regarding the patient risks posed by inpatient hyperglycemia, resistance to tighter control still exists. Barriers identified include lack of prescriber “ownership” of the problem if acute hyperglycemia is not the primary reason for hospital admission, prescriber’s perceptions that they lack skill in managing diabetes, fears of hypoglycemia, and inappropriate reliance on sliding-scale insulin regimens.

Continuous Improvement

Healthcare organizations can facilitate improved hospital glycemic control using several approaches, including the following: 1) gain institutional support to prioritize glycemic control; 2) establish a multidisciplinary team focused on achieving glycemic targets; 3) gather glycemic data and reliable metrics; 4) implement insulin prescribing protocols and order sets to standardize practice; and 5) create a comprehensive education program for health professionals and patients. A complete list of recommendations from the ADA for diabetes care in the hospital appears in Table 2.

The Joint Commission, in cooperation with the ADA, offers an Inpatient Diabetes Certificate of Distinction to recognize hospitals that implement critical attributes for successful diabetes programs, including specific staff education requirements, written blood glucose monitoring protocols, treatment plans for hypoglycemia and hyperglycemia, and patient education on self-management of diabetes.

Discharge Education

A significant percentage of medication errors occurs during the transition from hospital to home. Appropriate reconciliation of dismissal medications, including insulin regimens and/or other antidiabetic medications, is necessary for a safe transition and sustained control of hyperglycemia. Patients without a diagnosis of diabetes who experience acute hyperglycemia in the hospital should receive follow-up testing on an outpatient basis. A plan for continued diabetes education and follow-up should be discussed with the patient and included in patient discharge information.

Conclusion

An ever-increasing body of evidence supports targeted blood glucose control in the hospital setting, with the potential to improve patient morbidity and mortality. Hospital pharmacists are well positioned to play an important role in improving patient outcomes from hyperglycemia. Pharmacists can assist in breaking down barriers to improved glycemic control by educating healthcare providers on the risks of inpatient hyperglycemia and the appropriate use of insulin. They can play an active role in multidisciplinary committees to design and implement insulin order sets and protocols to enhance compliance with practice guidelines. Through daily blood glucose monitoring, pharmacists can assist the healthcare team in achieving desired glycemic control.


