American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control

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People with diabetes are more likely to be hospitalized and to have longer durations of hospital stay than those without diabetes. A recent survey estimated that 22% of all hospital inpatient days were incurred by people with diabetes and that hospital inpatient care accounted for half of the 174 billion USD total U.S. medical expenditures for this disease (1). These findings are due, in part, to the continued expansion of the worldwide epidemic of type 2 diabetes. In the U.S. alone, there are ~1.6 million new cases of diabetes each year, with an overall prevalence of 23.6 million people (7.8% of the population, with one-fourth of the cases remaining undiagnosed). An additional 57 million American adults are at high risk for type 2 diabetes (2). Although the costs of illness-related stress hyperglycemia are not known, they are likely to be considerable in light of the poor prognosis of such patients (3–6).

There is substantial observational evidence linking hyperglycemia in hospitalized patients (with or without diabetes) to poor outcomes. Cohort studies as well as a few early randomized controlled trials (RCTs) have suggested that intensive treatment of hyperglycemia improved hospital outcomes (5–8). In 2004, this evidence led the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE), in collaboration with the American Diabetes Association (ADA) and other medical organizations, to develop recommendations for treatment of inpatient hyperglycemia (9). In 2005, the ADA added recommendations for treatment of hyperglycemia in the hospital to its annual Standards of Medical Care (10). Recommendations from the ACE and the ADA generally endorsed tight glycemic control in critical care units. For patients in general medical and surgical units, where RCT evidence regarding treatment targets was lacking, glycemic goals similar to those advised for outpatients were advocated (9,10). In 2006, the ACE and the ADA partnered on a joint "call to action" for inpatient glycemic control, addressing a number of systematic implementation barriers in hospitals (11). These efforts contributed to a growing national movement viewing the management of inpatient hyperglycemia as a quality-of-care measure.

Although hyperglycemia is associated with adverse patient outcomes, intervention to normalize glycemia has yielded inconsistent results. Indeed, recent trials in critically ill patients have failed to show a significant improvement in mortality with intensive glycemic control (12,13) or have even shown increased mortality risk (14). Moreover, these recent RCTs have highlighted the risk of severe hypoglycemia resulting from such efforts (12–17). These outcomes have contributed to confusion regarding specific glycemic targets and the means for achieving them in both critically ill and noncritically ill patients.

Recognizing the importance of glycemic control across the continuum of care, the AACE and the ADA joined forces to develop this updated consensus statement on inpatient glycemic management. The central goals were to identify reasonable, achievable, and safe glycemic targets and to describe the protocols, procedures, and system improvements needed to facilitate their implementation. This document is addressed to health care professionals, supporting staff, hospital administrators, and other stakeholders focused on improved management of hyperglycemia in inpatient settings. Consensus panel members extensively reviewed the most current literature and considered the following questions:

1. Does improving glycemic control improve clinical outcomes for inpatients with hyperglycemia?
2. What glycemic targets can be recommended in different patient populations?
3. What treatment options are available for achieving optimal glycemic targets safely and effectively in specific clinical situations?

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4. Does inpatient management of hyperglycemia represent a safety concern?
5. What systems need to be in place to achieve these recommendations?
6. Is treatment of inpatient hyperglycemia cost-effective?
7. What are the optimal strategies for transition to outpatient care?
8. What are areas for future research?

QUESTION 1: DOES IMPROVING GLYCEMIC CONTROL IMPROVE CLINICAL OUTCOMES FOR INPATIENTS WITH HYPERGLYCEMIA?

— Hyperglycemia in hospitalized patients, irrespective of its cause, is unequivocally associated with adverse outcomes (5,6,18–25). Hyperglycemia occurs in patients with known or undiagnosed diabetes, or it occurs during acute illness in those with previously normal glucose tolerance (termed "stress hyperglycemia") (8,26).

Intervention directed at reducing blood glucose (BG) levels has resulted in improved outcomes in some, but not all, studies (5,18–25). Several recent clinical trials in critically ill patients have reported no reduction in mortality from intensive treatment targeting near-euglycemia versus conventional management targeting BG <180 mg/dl (<10.0 mmol/l). Of considerable concern are reports of harm, with higher rates of severe hypoglycemia and even increased mortality (14) resulting from intensive glycemic control (12–14,16,27,28). This variability in results may be attributable to several factors, including differences in intravenous (IV) insulin treatment protocols and their implementation, glycemic targets, patient populations, methods for glucose monitoring, and insulin adjustment (12,29).

The following section focuses primarily on results of recent studies with an RCT design that investigated patient outcomes with protocols targeting near-normalization of BG levels. Readers are referred to a previous ACE position statement (9), an ACE/ADA consensus statement (11), and a technical review (8) for details related to earlier studies supporting inpatient glycemic management.

Data derived from surgical and medical intensive care units

Observational studies have documented that hyperglycemia after cardiothoracic surgical procedures is associated with higher rates (approximately twofold) of wound infection (20,30). Interventions to reduce hyperglycemia in this setting with IV insulin therapy decrease infection rates (19,21,31) and cardiac-related mortality (5,32), in comparison with historical control subjects.

The results of several RCTs conducted in critically ill patients in medical and surgical intensive care units (ICUs) are summarized in Table 1 (5,13,14,16,27,28,33–36). Intensive insulin therapy targeting arterial glucose levels of 80–110 mg/dl (4.4–6.1 mmol/l) in a surgical ICU patient population resulted in a significant decrease in morbidity and mortality (5). However, implementation of the identical protocol in 1,200 medical ICU patients by the same investigators in the same institution diminished morbidity but failed to reduce mortality. A sixfold increase in severe hypoglycemic events (BG <40 mg/dl [2.2 mmol/l]) was observed in the intensively treated group (18.7 vs. 3.1%), and hypoglycemia was identified as an independent risk factor for mortality (16).

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study reported no decrease in mortality and higher rates of severe hypoglycemia with intensive insulin therapy in patients with severe sepsis (17 vs. 4.1%; $P < 0.001$) (13). Hypoglycemia—BG <40 mg/dl (<2.2 mmol/l)—was identified as an independent risk factor for mortality (relative risk, 2.2 at 28 days; 95% CI, 1.6 to 3.0) (Dr. Frank Brunkhorst [Jena University Hospital, Jena, Germany], personal communication). Similarly, intensive glycemic control in a mixed medical and surgical ICU resulted in no decrease in morbidity or mortality, while increasing the rate of hypoglycemia fivefold (28).

The largest study to date, Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multicenter, multinational RCT, tested the effect of tight glycemic control on outcomes among 6,104 critically ill participants, the majority of whom (>95%) required mechanical ventilation (14). The 90-day mortality was significantly higher in the intensively treated versus the conventionally treated group (78 more deaths; 27.5 vs. 24.9%; $P = 0.02$) in both surgical and medical patients. Mortality from cardiovascular causes was more common in the intensively treated group (76 more deaths; 41.6 vs. 35.8%; $P = 0.02$). Severe hypoglycemia was also more common in the intensively treated group (6.8 vs. 0.5%; $P < 0.001$).

A recent meta-analysis of RCTs reported comparisons between intensive insulin therapy with glycemic targets of 72–126 mg/dl (4.0–7.0 mmol/l) (commonly, 80 to 110 mg/dl [4.4–6.1 mmol/l]) and less intensive therapy with targets of <150 to 220 mg/dl (<8.3–12.2 mmol/l) (commonly, 180 to 200 mg/dl [10.0–11.1 mmol/l]). Among 8,432 critically ill patients, there was no significant difference in mortality between intensive therapy and control groups (21.6 vs. 23.3%, respectively) (12). A decrease in septicemia and a fivefold increase in hypoglycemia (13.7 vs. 2.5%) were observed. In a second meta-analysis (17) including 13,567 critically ill patients, a favorable effect of intensive therapy on mortality was noted only in surgical ICU patients (relative risk, 0.63; CI, 0.44 to 0.91). There was a sixfold increase in the rate of occurrence of hypoglycemia with use of intensive therapy in all ICU patients (17).

The higher rates of severe hypoglycemia associated with intensive insulin therapy (12–14,16,27,28) raise the possibility that serious adverse events in the subgroup of patients experiencing hypoglycemia offset, at least in part, any benefit derived from strict glycemic control in the much larger subgroup of patients without hypoglycemic events (13,16). Hypoglycemic events, however, have been infrequently linked to mortality; this finding suggests that severe hypoglycemia may be a marker of more serious underlying disease (13,14,16).

Data derived from patients with acute myocardial infarction

Although hyperglycemia is associated with adverse outcomes after acute myocardial infarction (AMI) (37–41), reduction of glycemia per se, and not necessarily the use of insulin, is associated with improved outcomes (7). It remains unclear, however, whether hyperglycemia is a marker of underlying health status or is a mediator of complications after AMI. Noniatrogenic hypoglycemia has also been associated with adverse outcomes and is a predictor of higher mortality (7,42,43).

Several studies have attempted to reproduce the favorable outcomes observed with early implementation of insulin therapy reported in the first Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial (33).

Table 1—*Summary data of selected randomized controlled trials of intensive insulin therapy in critically ill patients (>200 randomized patients)*[a]

Trial	*N*	Setting	Blood glucose target [mg/dl (mmol/l)]		Blood glucose achieved [mg/dl (mmol/l)][b]		Primary outcome	End point rate (%)		ARR (%)[c]	RRR (%)[c]	Odds ratio (95% CI)
			Intensive	Conventional	Intensive	Conventional		Intensive	Conventional			
DIGAMI (ref. 33), 1995	620	CCU (AMI)	126–196 (7–10.9)	Usual care	173 (9.6)	211 (11.7)	1-year mortality	18.6	26.1	7.5	29[d]	NR
Van den Berghe et al. (ref. 5), 2001	1,548	SICU	80–110 (4.4–6.1)	180–200 (10–11)	103 (5.7)	153 (8.5)	ICU mortality	4.6	8.0	3.4	42	0.58 (0.38–0.78)[d]
DIGAMI 2 (ref. 34), 2005	1,253	CCU (AMI)	126–180 (7–10) (groups 1 and 2)	Usual care (group 3)	164 (9.1)	180 (10)	2-year mortality	Group 1, 23.4; group 2, 21.2	Group 3, 17.9	—[e]	—[e]	NR
Van den Berghe et al. (ref. 16), 2006	1,200	MICU	80–110 (4.4–6.1)	180–200 (10–11)	111 (6.2)	153 (8.5)	Hospital mortality	37.3	40.0	2.7	7.0	0.94 (0.84–1.06)[e]
HI-5 (ref. 35), 2006	240	CCU (Ami) (GIK)	72–180 (4–10)	Usual care <288	149 (8.3)	162 (9)	6-month mortality	7.9	6.1	−1.8[e]	−30[e]	NR
GluControl (ref. 27), 2007[f]	1,101	ICU	80–110 (4.4–6.1)	140–180 (7.8–10)	118 (6.5)	144 (8)	ICU mortality	16.7	15.2	−1.5	−10	1.10 (0.84–1.44)[e]
Gandhi et al. (ref. 36), 2007	399	Operating room	80–110 (4.4–6.1)	<200 (<11)	114 (6.3)	157 (8.7)	Composite[g]	44	46	2	4.3	1.0 (0.8–1.2)[e]
VISEP (ref. 13), 2008	537[h]	ICU	80–110 (4.4–6.1)	180–200 (10–11)	112 (6.2)	151 (8.4)	28-day mortality	24.7	26.0	1.3	5.0	0.89 (0.58–1.38)[e,i]
De La Rosa et al. (ref. 28), 2008[f]	504	SICU MICU	80–110 (4.4–6.1)	180–200 (10–11)	117 (6.5)	148 (8.2)	28-day mortality	36.6	32.4	−4.2[e]	−13[e]	NR
NICE-SUGAR (ref. 14), 2009	6,104	ICU	81–108 (4.5–6)	≤180 (≤10)	115 (6.4)	145 (8.0)	3-month mortality	27.5	24.9	−2.6	−10.6	1.14 (1.02–1.28)[d]

[a]ARR, absolute risk reduction; CCU, coronary care unit; GIK, glucose-insulin-potassium; MICU, medical ICU; NR, not reported; RRR, relative risk reduction; SICU, surgical ICU. [b]Mean morning blood glucose concentrations (except for GluControl, which reported mean overall blood glucose concentrations). [c]Intensive group versus conventional group. [d]$P < 0.05$. [e]Not significant ($P > 0.05$). [f]Presented as abstract only. [g]Composite of death, sternal infection, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure at 30 days. [h]Only patients with sepsis. [i]Personal communication, Dr. Frank Brunkhorst.

DIGAMI 2, a multicenter RCT of 1,253 patients with AMI and diabetes, failed to show a decrease in mortality with such intervention (34). The Hyperglycemia Intensive Insulin Infusion in Infarction (HI-5) study randomly assigned patients with AMI to 24-h infusions of insulin plus glucose for 24 h (BG goal <180 mg/dl [<10.0 mmol/l]) or usual care. There were no significant differences in mortality, although there was a decreased incidence of congestive heart failure and reinfarction at 3 months in the intensively treated group (35). The very large Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latin America (CREATE-ECLA), with 20,201 patients, tested the efficacy of glucose-insulin-potassium infusion in post-AMI patients and found no decrease in mortality (44). A failure to achieve a prespecified glycemic target with intensive therapy that differed from those in the control group may have contributed to these negative results (34,44).

Data derived from other critically ill patients

Several retrospective studies have examined the relationship between glycemia and clinical outcomes in patients with extensive burns, body trauma, or traumatic brain injury or who have undergone surgical treatment for cerebral aneurysms (45–53). In patients with subarachnoid hemorrhage, hyperglycemia was associated with impaired cognition and deficits in gross neurologic function at 3 months (52). Patients without diabetes who had severe blunt injury and hyperglycemia (BG >200 mg/dl [11.1 mmol/l]) were found to have a 2.2-fold higher rate of mortality than those with admission glucose of <200 mg/dl (11.1 mmol/l) (54). Similar findings have been reported by some investigators (55,56) but not others (57,58). In an RCT of tight glycemic control in 97 patients with severe traumatic brain injury (59), no significant differences were noted in infections, 6-month mortality, or neurologic outcomes. The rate of occurrence of hypoglycemia was twofold higher with use of intensive insulin therapy.

Data derived from patients undergoing transplantation

Diabetes in patients after transplant procedures shares many similarities with type 2 diabetes and is strongly associated with cardiovascular disease and cardiac death (60). Fuji et al. (61). examined the effects

of hyperglycemia during neutropenic periods in 112 patients undergoing stem cell transplantation. Hyperglycemia was associated with risk of organ failure, grades II–IV acute graft-versus-host disease, and non–relapse-related mortality, but not with infection or fever. A similar study in 382 patients reported that in those patients not treated with glucocorticoids during neutropenia, each 10 mg/dl (0.6 mmol/l) increase in BG was associated with a 1.15-fold increase in the odds ratio for bacteremia (62). Hammer et al. (63) analyzed BG levels among 1,175 adult patients receiving allogeneic hematopoietic cell transplants. Hyperglycemia, hypoglycemia, and glycemic variability all correlated with non–relapse-related mortality within 200 days after transplantation.

Data derived from studies on intraoperative glycemic management

In a double-blind, placebo-controlled RCT involving 82 adults, intraoperative glucose-insulin-potassium infusion during a coronary artery bypass grafting procedure did not reduce myocardial damage, mortality, or length of stay (LOS) (64). In a study of 399 patients undergoing cardiac surgical procedures, intensive insulin therapy (target BG, 80–100 mg/dl [4.4–5.6 mmol/l]) intraoperatively resulted in no difference in patient outcomes; postoperatively, however, both groups were treated to similar glycemic targets (36).

Data derived from pediatric ICUs

Although outside the scope of this consensus statement, it is worth noting that hyperglycemia (without diabetes) is also common among pediatric patients with critical illness (65–70), and it correlates with mortality (70). An international, multicenter RCT, which tested the effect of intensive glycemic control in very-low-birth-weight neonates, found higher rates of severe hypoglycemia and no significant difference in mortality or morbidity (71). In contrast, another randomized trial conducted among 700 critically ill infants (n = 317) and children (n = 383) reported decreases in mortality, inflammatory markers, and LOS with use of intensive insulin therapy, despite a greater frequency of severe hypoglycemia (25 vs. 5%) (72).

Hyperglycemia in hospitalized medical and surgical patients in non-ICU settings

No RCTs have examined the effect of intensive glycemic control on outcomes in hospitalized patients outside ICU settings. Several observational studies, however, point to a strong association between hyperglycemia and poor clinical outcomes, including prolonged hospital stay, infection, disability after discharge from the hospital, and death (4,7,35,73–81).

Several studies have found glucose variability to be an independent predictor of mortality in critically ill patients (63,66,82). Whether intervention to control glycemic variability, per se, improves outcomes is not known (83).

Summary of clinical trials reviewed for question 1

Overall, although a very tight glucose target (80–110 mg/dl [4.4–6.1 mmol/l]) was beneficial in a predominantly surgical ICU population (5), this target has been difficult to achieve in subsequent studies, including the recently published NICE-SUGAR study (14), without increasing the risk for severe hypoglycemia (12, 13,16,27,28). In addition, there has been no consistent reduction in mortality with intensive control of glycemia (12,17), and increased mortality was observed in the largest published study to date (14). The reasons for this inconsistency are not entirely clear. The positive results reported in the initial studies may have been attributable to differences in measurement and reporting of BG values, selection of participants, glycemic variability, or nutritional support (12,17,84). Nevertheless, recent attempts to achieve tight glycemic control either have not reduced or have actually increased mortality in multicenter trials and clearly led to higher rates of hypoglycemia (13,14,16).

Despite the inconsistencies, it would be a serious error to conclude that judicious control of glycemia in critically ill patients, and in non-ICU patients in general, is not warranted. First, on the basis of a large number of studies in a variety of inpatient settings, uncontrolled hyperglycemia clearly is associated with poor outcomes. Second, although severe hypoglycemic events are observed in an unacceptably high number of patients receiving intensive insulin therapy with protocols targeting a BG of 80–110 mg/dl (4.4–6.1 mmol/l) (12), this risk can likely be minimized with relaxation of targets, improvement and standardization of protocols, and their careful implementation. Third, perhaps major beneficial effects on outcomes can be derived from a higher target range of glucose than 80–110 mg/dl in comparison with uncontrolled hyperglycemia.

Finally, until further information becomes available, it is prudent to continue to emphasize the importance of glycemic control in hospitalized patients with critical and noncritical illness while aiming at targets that are less stringent than 80–110 mg/dl (4.4–6.1 mmol/l), a topic that is discussed in detail subsequently.

QUESTION 2: WHAT GLYCEMIC TARGETS CAN BE RECOMMENDED IN DIFFERENT PATIENT POPULATIONS?

— The management of hyperglycemia in the hospital presents unique challenges that stem from variations in a patient's nutritional status and level of consciousness, the practical limitations of intermittent glycemic monitoring, and the ultimate importance of patient safety. Accordingly, reasonable glucose targets in the hospital setting are modestly higher than may be routinely advised for patients with diabetes in the outpatient setting (85,86).

Definition of glucose abnormalities

In this report, hyperglycemia is defined as any BG value >140 mg/dl (>7.8 mmol/l). Levels that are significantly and persistently above this level may necessitate treatment in hospitalized patients. In patients without a previous diagnosis of diabetes, elevated BG concentrations may be due to stress hyperglycemia, a condition that can be established by a review of prior medical records or measurement of A1C. A1C values of >6.5–7.0% suggest that diabetes preceded hospitalization (87).

Hypoglycemia is defined as any BG level <70 mg/dl (<3.9 mmol/l) (88). This is the standard definition in outpatients and correlates with the initial threshold for the release of counterregulatory hormones (89). Severe hypoglycemia in hospitalized patients has been defined by many clinicians as <40 mg/dl (<2.2 mmol/l), although this value is lower than the approximate 50 mg/dl (2.8 mmol/l) level at which cognitive impairment begins in normal individuals (89–91). As with hyperglycemia, hypoglycemia among inpatients is also associated with adverse short-term and long-term outcomes. Early recognition and treatment of mild to moderate hypoglycemia (40 and 69 mg/dl [2.2 and 3.8 mmol/l], respectively) can prevent deterioration to a more severe ep-

isode with potential adverse sequelae (91,92).

Treatment of hyperglycemia in critically ill patients

On the basis of the available evidence, insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 180 mg/dl (10.0 mmol/l). Once IV insulin therapy has been initiated, the glucose level should be maintained between 140 and 180 mg/dl (7.8 and 10.0 mmol/l). Greater benefit may be realized at the lower end of this range. Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients. Targets <110 mg/dl (6.1 mmol/l), however, are not recommended. Use of insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of occurrence of hypoglycemia, is highly recommended.

Treatment of hyperglycemia in noncritically ill patients

With no prospective, RCT data for establishing specific guidelines in noncritically ill patients, our recommendations are based on clinical experience and judgment. For the majority of noncritically ill patients treated with insulin, premeal glucose targets should generally be <140 mg/dl (<7.8 mmol/l) in conjunction with random BG values <180 mg/dl (<10.0 mmol/l), as long as these targets can be safely achieved. For avoidance of hypoglycemia, consideration should be given to reassessing the insulin regimen if BG levels decline below 100 mg/dl (5.6 mmol/l). Modification of the regimen is necessary when BG values are <70 mg/dl (<3.9 mmol/l), unless the event is easily explained by other factors (such as a missed meal).

Occasional clinically stable patients with a prior history of successful tight glycemic control in the outpatient setting may be maintained with a glucose range below the aforementioned cut points. In contrast, higher glucose ranges may be acceptable in terminally ill patients or in patients with severe comorbidities, as well as in those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible.

We emphasize that clinical judgment in combination with ongoing assessment of the patient's clinical status, including changes in the trajectory of glucose measures, the severity of illness, the nutritional status, or the concurrent use of medications that might affect glucose levels (for example, corticosteroids or octreotide), must be incorporated into the day-to-day decisions regarding insulin dosing (93,94).

Inpatient glucose metrics

Hospitals attempting to improve the quality of their glycemic control and clinical investigators who analyze glycemic management require standardized glucose measures for assessment of baseline performance and the effect of any intervention (11). Several methods have been proposed for determining the adequacy of glycemic control across a hospital or unit. A recent study indicated that a simple measure of mean BG (39) provides information similar to that from more complex metrics (hyperglycemic index, time-averaged glucose) (14,48). The "patient-day" unit of measure is another proposed metric of hospital glucose data, especially when there is substantial variability in the duration of hospital stay (95). The patient-day metric may yield a more accurate assessment of the frequency of hypoglycemia and severe hyperglycemic events, providing an approach for obtaining measures of performance for clinical investigation (95).

The absolute definition of high-quality BG control has not been determined. Of course, one should aim for the highest percentage of patients within a prespecified BG target range. The opposite holds true for hypoglycemia. What is reasonable for a hospital to achieve and with what consistency have not been studied, and information regarding best practices in this area is needed.

QUESTION 3: WHAT TREATMENT OPTIONS ARE AVAILABLE FOR ACHIEVING OPTIMAL GLYCEMIC TARGETS SAFELY AND EFFECTIVELY IN SPECIFIC CLINICAL SITUATIONS?

— In the hospital setting, insulin therapy is the preferred method for achieving glycemic control in most clinical situations (8). In the ICU, IV infusion is the preferred route of insulin administration. Outside of critical care units, subcutaneous administration of insulin is used much more frequently. Orally administered agents have a limited role in the inpatient setting.

IV insulin infusions

In the critical care setting, continuous IV insulin infusion has been shown to be the most effective method for achieving specific glycemic targets (8). Because of the very short half-life of circulating insulin, IV delivery allows rapid dosing adjustments to address alterations in the status of patients.

IV insulin therapy is ideally administered by means of validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and insulin dose. An extensive review of the merits and deficiencies of published protocols is beyond the intent of this statement, and readers are referred to several available reports and reviews (96–101). Continued education of staff in conjunction with periodic ongoing review of patient data is critical for successful implementation of any insulin protocol (97–101).

Patients who receive IV insulin infusions will usually require transition to subcutaneously administered insulin when they begin eating regular meals or are transferred to lower-intensity care. Typically, a percentage (usually 75–80%) of the total daily IV infusion dose is proportionately divided into basal and prandial components (see subsequent material). Importantly, subcutaneously administered insulin must be given 1–4 h before discontinuation of IV insulin therapy in order to prevent hyperglycemia (102). Despite these recommendations, a safe and effective transition regimen has not been substantiated.

Subcutaneously administered insulin

Scheduled subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycemia. The recommended components of inpatient subcutaneous insulin regimens are a basal, a nutritional, and a supplemental (correction) element (8,103). Each component can be met by one of several available insulin products, depending on the particular hospital situation. Readers are referred to several recent publications and reviews that describe currently available insulin preparations and protocols (101–106).

A topic that deserves particular attention is the persistent overuse of what has been branded as sliding scale insulin (SSI) for management of hyperglycemia. The term "correction insulin," which refers to

the use of additional short- or rapid-acting insulin in conjunction with scheduled insulin doses to treat BG levels above desired targets, is preferred (8). Prolonged therapy with SSI as the sole regimen is ineffective in the majority of patients (and potentially dangerous in those with type 1 diabetes) (106–112).

Noninsulin agents

Noninsulin agents are inappropriate in most hospitalized patients. Continued use of such agents may be appropriate in selected stable patients who are expected to consume meals at regular intervals. Caution must be exercised with use of metformin because of the potential development of a contraindication during the hospitalization, such as renal insufficiency, unstable hemodynamic status, or need for imaging studies with radiocontrast dye (8,113). Injectable noninsulin therapies such as exenatide and pramlintide have limitations similar to those with orally administered agents in the hospital setting.

Specific clinical situations

Patients using an insulin pump. Patients who use continuous subcutaneous insulin infusion (pump) therapy in the outpatient setting can be candidates for diabetes self-management in the hospital, provided they have the mental and physical capacity to do so (8,103,114,115). Of importance, nursing personnel must document basal rates and bolus doses on a regular basis (at least daily). The availability of hospital personnel with expertise in continuous subcutaneous insulin infusion therapy is essential (115).

Patients receiving enteral nutrition. Hyperglycemia is a common side effect of inpatient enteral nutrition therapy (116,117). A recent study, in which a combination of basal insulin and correction insulin was used, achieved a mean glucose value of 160 mg/dl (8.9 mmol/l). Similar results were achieved in the group randomized to receive SSI only; however, 48% of patients required the addition of intermediate-acting insulin to achieve glycemic targets (109).

Patients receiving parenteral nutrition. The high glucose load in standard parenteral nutrition frequently results in hyperglycemia, which is associated with a higher incidence of complications and mortality in critically ill patients in the ICU (118). Insulin therapy is highly recommended, with glucose targets as defined previously on the basis of the severity of illness.

Patients receiving glucocorticoid therapy. Hyperglycemia is a common complication of corticosteroid therapy (93). Several approaches have been proposed for treatment of this condition, but no published protocols or studies have investigated the efficacy of these approaches. A reasonable approach is to institute glucose monitoring for at least 48 h in all patients receiving high-dose glucocorticoid therapy and to initiate insulin therapy as appropriate (94). In patients who are already being treated for hyperglycemia, early adjustment of insulin doses is recommended (119). Importantly, during corticosteroid tapers, insulin dosing should be proactively adjusted to avoid hypoglycemia.

QUESTION 4: DOES INPATIENT MANAGEMENT OF HYPERGLYCEMIA REPRESENT A SAFETY CONCERN?

— Overtreatment and undertreatment of hyperglycemia represent major safety issues in hospitalized patients with and without diabetes (90,120,121). Fear of hypoglycemia, clinical inertia, and medical errors are major barriers to achieving optimal blood glucose control (90,122–131). In most clinical situations, safe and reasonable glycemic control can be achieved with appropriate use of insulin, adjusted according to results of bedside glucose monitoring (102,106,109).

Clinical situations that increase the risk for hypoglycemia and hyperglycemia in the hospital include the following:

1. Changes in caloric or carbohydrate intake ("nothing by mouth" status, enteral nutrition, or parenteral nutrition) (94,128)
2. Change in clinical status or medications (for example, corticosteroids or vasopressors) (93,98)
3. Failure of the clinician to make adjustments to glycemic therapy based on daily BG patterns (102,128)
4. Prolonged use of SSI as monotherapy (107,108)
5. Poor coordination of BG testing and administration of insulin with meals (121,129)
6. Poor communication during times of patient transfer to different care teams (120,121)
7. Use of long-acting sulfonylureas in elderly patients and those with kidney or liver insufficiency
8. Errors in order writing and transcription (102,120)

Hypoglycemia is a major safety concern with use of insulin and insulin secretagogues. Hypoglycemia can occur spontaneously in patients with sepsis (130) or in patients who receive certain medications, including quinolone antibiotics and β-adrenergic agonists. Although not all hypoglycemic episodes are avoidable, the use of nurse-driven hypoglycemia treatment protocols that prompt early therapy for any BG levels <70 mg/dl (<3.9 mmol/l) can prevent deterioration of potentially mild events—for example, BG values of 60–69 mg/dl (3.3–3.8 mmol/l)—to more severe events—for example, BG concentrations <40 mg/dl (<2.2 mmol/l) (88,90–92,98,131). Particular attention is required in high-risk patients, including those with malnutrition; advanced age; a history of severe hypoglycemia (88,132); or autonomic, kidney, liver, or cardiac failure.

Clinical inertia can be defined as not adjusting glycemic therapy in response to persistently abnormal results on BG determination (123). Often, there is a lack of ownership for diabetes management, particularly in hospitalized patients admitted with a primary diagnosis other than diabetes (128). This inaction may be due in part to insufficient knowledge or confidence in diabetes management (123,133). Improvements in care can be achieved by ongoing education and training (134,135).

Insulin errors

Insulin has consistently been designated as a high-alert medication because of the risk of harm that can accompany errors in prescribing, transcribing, or dosing (136). The true frequency of such errors is unknown because the available data sources depend on voluntary reporting of errors (102,137) and mechanisms for real-time root-cause analysis are not available in most hospitals.

BG monitoring

Bedside BG monitoring with use of point-of-care (POC) glucose meters is performed before meals and at bedtime in most inpatients who are eating usual meals. It is important to avoid routine use of correction insulin at bedtime. In patients who are receiving continuous enteral or parenteral nutrition, glucose

monitoring is optimally performed every 4–6 h. In patients who are receiving cycled enteral nutrition or parenteral nutrition, the schedule for glucose monitoring can be individualized but should be frequent enough to detect hyperglycemia during feedings and the risk of hypoglycemia when feedings are interrupted (109,112). More frequent BG testing, ranging from every 30 min to every 2 h, is required for patients receiving IV insulin infusions.

Glucose meters

Safe and rational glycemic management relies on the accuracy of BG measurements performed with use of POC glucose meters, which have several important limitations. Although the U.S. Food and Drug Administration allows a 20% error for glucose meters, questions have been raised about the appropriateness of this criterion (138). Glucose measurements differ significantly between plasma and whole blood, terms that are often used interchangeably and can lead to misinterpretation. Most commercially available capillary glucose meters introduce a correction factor of ~1.12 to report a "plasma adjusted" value (139).

Significant discrepancies among capillary, venous, and arterial plasma samples have been observed in patients with low or high hemoglobin concentrations, hypoperfusion, or the presence of interfering substances (139,140). Analytical variability has been described with several POC glucose meters (141). Any glucose result that does not correlate with the patient's clinical status should be confirmed through conventional laboratory sampling of plasma glucose.

Although laboratory measurement of plasma glucose has less variability and interference, multiple daily phlebotomies are not practical. Moreover, the use of indwelling lines as the sampling source poses risks for infection. Studies performed with use of continuous interstitial glucose-monitoring systems in the critical care setting (142,143) currently are limited by the lack of reliability of BG measurements in the hypoglycemic range as well as by cost.

QUESTION 5: WHAT SYSTEMS NEED TO BE IN PLACE TO ACHIEVE THESE RECOMMENDATIONS?

— The complexity of inpatient glycemic management necessitates a systems approach that facilitates safe practices and reduces the risk for errors (120,121). Systems that facilitate the appropriate use of scheduled insulin therapy, with institutional support for inpatient personnel who are knowledgeable in glycemic management, are essential for achieving safe and reasonable levels of glycemic control in hospitalized patients. Readers are referred to the 2006 ACE/ADA consensus statement, which outlines the systems that must be in place to promote effective glycemic management in the hospital (11). Some of these recommendations are reviewed briefly in the following paragraphs.

The success of any glycemic management program depends on the ability to obtain financial support from hospital administrators, who should be made aware of the potential for cost savings with reductions in morbidity, durations of hospital stay, and need for readmission. This support is necessary for covering the costs of staff education, equipment, and personnel to oversee an inpatient diabetes management program (144).

The creation of a multidisciplinary steering committee guided by local diabetes experts can establish reasonable and achievable glycemic management goals with use of protocols and order sets (90). Preprinted order sets or computerized ordering systems with adequate technical support are useful tools for facilitating appropriate glycemic therapy (8,11,145). These tools can advance orders that contain contingencies that promote patient safety, such as withholding prandial insulin if a patient will not eat (102). Protocols need to be reviewed periodically and revised in accordance with available evidence.

Inpatient providers often have insufficient knowledge about the many aspects of inpatient diabetes care (133). Thus, education of personnel is essential, especially early during the implementation phase (101,127). Formal communication among various disciplines and services helps to garner support from hospital personnel for new practices and protocols, as well as providing a venue for identifying concerns.

Many hospitals are challenged by poor coordination of meal delivery and prandial insulin administration (130), as well as variability in the carbohydrate content of meals (94). Ensuring appropriate administration of insulin with respect to meals despite variations in food delivery necessitates coordination between dietary and nursing services (122). A systems approach can also promote the coordination of glucose monitoring, insulin administration, and meal delivery, particularly during change of shifts and times of patient transfer (121,122).

Electronic health records and computerized physician order entry systems have the potential to improve the sharing of information, including POC glucose results and associated medication administration—which can contribute to the reduction of medical errors. These systems can also provide access to algorithms, protocols, and decision support tools that can help guide therapy (146,147).

QUESTION 6: IS TREATMENT OF INPATIENT HYPERGLYCEMIA COST-EFFECTIVE?

— A program of inpatient glycemic control with prespecified glycemic targets will have associated costs attributable to an increase in time needed from physicians, nurses, pharmacists, and other services. These costs are best viewed as short-term investments that ultimately provide long-term cost savings because of improved clinical outcomes, with observed decreases in LOS, inpatient complications, and need for rehospitalization (148–155).

Pharmacoeconomic analyses have examined the cost-effectiveness of improved glycemic control in the hospital setting (148,149). In the Portland Diabetic Project, a 17-year prospective nonrandomized study of 4,864 patients with diabetes who underwent open-heart surgical procedures, institution of continuous IV insulin therapy to achieve predetermined target BG levels reduced the incidence of deep sternal wound infections by 66%, resulting in a total net savings to the hospital of 4,638 USD per patient (148). In another study, intensive glycemic control in 1,600 patients treated in a medical ICU was associated with a total cost savings of 1,580 USD per patient (149). Van den Berghe et al. (150) reported cost savings of 3,476 USD per patient by strict normalization of BG levels with use of a post hoc health care resource utilization analysis of their randomized mechanically ventilated surgical ICU patients. In a retrospective analysis of patients undergoing coronary artery bypass grafting, each 50 mg/dl (2.8 mmol/l) increase in BG values on the day of and after the surgical procedure was associated with an increase in hospital cost of 1,769 USD and an increase in duration of hospital stay of 0.76 days (151). In a tertiary care trauma center, implementation

of a diabetes management program to reduce the monthly mean BG level by 26 mg/dl (1.4 mmol/l) (177–151 mg/dl [9.8–8.4 mmol/l]) resulted in significant reductions in LOS (0.26 days) in association with estimated hospital savings of more than two million USD per year (152). In another study, implementation of a subcutaneous insulin protocol for treatment of patients with hyperglycemia in the emergency department resulted in a subsequent reduction of hospital stay by 1.5 days (153).

The use of an intensified inpatient protocol by a diabetes management team resulted in correct coding and treatment of patients with previously unrecognized hyperglycemia. The LOS was reduced for both primary and secondary diagnoses of diabetes, and readmission rates declined (154). In a different study, the use of diabetes team consultation resulted in a 56% reduction in LOS and a cost reduction of 2,353 USD per patient (155).

Thus, intensive glycemic control programs have reported substantial cost savings, primarily attributable to decreases in laboratory, pharmacy, and radiology costs; fewer inpatient complications; decreased ventilator days; and reductions in ICU and hospital LOS. These reports demonstrate that optimization of inpatient glycemic management not only is effective in reducing morbidity and mortality but also is cost-effective. The business case for hospital support of glycemic management programs is based on opportunities for improving the accuracy of documentation and coding for diabetes-related diagnoses. The case for revenue generation through billing for clinical services is based on opportunities to increase the provision of glycemic management services in the hospital. It is imperative to involve hospital administration in providing the necessary financial support for inpatient glycemic management programs that will ultimately result in cost savings in conjunction with improved patient outcomes.

QUESTION 7: WHAT ARE THE OPTIMAL STRATEGIES FOR TRANSITION TO OUTPATIENT CARE?

— Preparation for transition to the outpatient setting is an important goal of inpatient diabetes management and begins with the hospital admission. This entails a fundamental shift in responsibility from a situation in which hospital personnel provide the diabetes care to one in which the patient is capable of self-management. Successful coordination of this transition requires a team approach that may involve physicians, nurses, medical assistants, dietitians, case managers, and social workers (8). Hospitals with certified diabetes educators benefit from their expertise during the discharge process.

Admission assessment obtains information regarding any prior history of diabetes or hyperglycemia, its management, and the level of glycemic control. Early assessment of a patient's cognitive abilities, literacy level, visual acuity, dexterity, cultural context, and financial resources for acquiring outpatient diabetic supplies allows sufficient time to prepare the patient and address problem areas.

Hospitalization provides a unique opportunity for addressing a patient's education in diabetes self-management (3). Because the mean hospital LOS is usually <5 days (2) and the capacity to learn new material may be limited during acute illness, diabetes-related education is frequently limited to an inventory of basic "survival skills."

It is recommended that the following areas be reviewed and addressed before the patient is discharged from the hospital (8):

- Level of understanding related to the diagnosis of diabetes
- Self-monitoring of BG and explanation of home BG goals
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia
- Identification of health care provider who will be responsible for diabetes care after discharge
- Information on consistent eating patterns
- When and how to take BG-lowering medications, including administration of insulin (if the patient is receiving insulin for ongoing management at home)
- Sick day management
- Proper use and disposal of needles and syringes

Medication errors and adverse drug events have been linked to poor communication of instructions to the patient at the time of discharge (156,157). This is particularly true for insulin regimens, which are inherently more complex. Because the day of discharge is not always conducive to retention of verbal instructions (158), clearly written instructions provide a reference for patients and their outpatient providers, and they provide a format for medication reconciliation between inpatient and outpatient settings. In one recent study, an insulin-specific discharge instruction form provided greater clarity and more consistent directions for insulin dosing and self-testing of BG in comparison with a generic hospital discharge form (159).

An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes educator within 1 month after discharge from the hospital is advised for all patients having hyperglycemia in the hospital (8). Clear communication with outpatient providers either directly or by means of hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the cause or the plan for determining the cause of hyperglycemia, related complications and comorbidities, and recommended treatments can assist outpatient providers as they assume ongoing care.

QUESTION 8: WHAT ARE AREAS FOR FUTURE RESEARCH?

— The following are selected research topics and questions proposed for guiding the management of patients with hyperglycemia in various hospital settings.

Stress hyperglycemia

- What are the underlying mechanisms?
- What abnormalities lead to variability in insulin resistance observed in some critically ill patients?
- What therapeutic modalities, in addition to glycemic control, would improve outcomes in critically ill patients with hyperglycemia?
- Are there optimal and safe glycemic targets specific to certain populations of critically ill patients?

Severe hypoglycemia

- What is the profile of inpatients at greatest risk for severe hypoglycemia?
- What are the short-term and long-term outcomes of patients experiencing severe hypoglycemia?
- What are the true costs of inpatient hypoglycemia?

Glycemic targets on general medical and surgical wards

- What are optimal and safe glycemic targets in noncritically ill patients on medical and surgical wards? Recommended end points for an RCT include rates of hypoglycemia, hospital-acquired infec-

tions, other in-hospital complications, LOS, and readmission.

Glycemic variability
- What is the effect of glycemic variability and the rate of change in glycemia on short-term and long-term outcomes, both in ICU and non-ICU settings?

Hospital systems and safety
- What hospital systems and safety measures are important for improving glycemic control and patient outcomes?
- What teams and support systems are required for safe and effective transition of patients to the outpatient setting?

Insulin treatment and monitoring instruments
- What are safe and effective strategies for inpatient use of insulin and insulin analogues?
- What is the role of continuous glucose-monitoring systems in inpatient settings?

Pediatric inpatient populations
- What are the optimal and safe glycemic targets in noncritically ill hospitalized children?

SUMMARY OF RECOMMENDATIONS

I. Critically ill patients
- Insulin therapy should be initiated for treatment of persistent hyperglycemia, starting at a threshold of no greater than 180 mg/dl (10.0 mmol/l).
- Once insulin therapy has been started, a glucose range of 140–180 mg/dl (7.8–10.0 mmol/l) is recommended for the majority of critically ill patients.
- Intravenous insulin infusions are the preferred method for achieving and maintaining glycemic control in critically ill patients.
- Validated insulin infusion protocols with demonstrated safety and efficacy, and with low rates of occurrence of hypoglycemia, are recommended.
- With IV insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control.

II. Noncritically ill patients
- For the majority of noncritically ill patients treated with insulin, the premeal BG target should generally be <140 mg/dl (<7.8 mmol/l) in conjunction with random BG values <180 mg/dl (<10.0 mmol/l), provided these targets can be safely achieved.
- More stringent targets may be appropriate in stable patients with previous tight glycemic control.
- Less stringent targets may be appropriate in terminally ill patients or in patients with severe comorbidities.
- Scheduled subcutaneous administration of insulin, with basal, nutritional, and correction components, is the preferred method for achieving and maintaining glucose control.
- Prolonged therapy with SSI as the sole regimen is discouraged.
- Noninsulin antihyperglycemic agents are not appropriate in most hospitalized patients who require therapy for hyperglycemia.
- Clinical judgment and ongoing assessment of clinical status must be incorporated into day-to-day decisions regarding treatment of hyperglycemia.

III. Safety issues
- Overtreatment and undertreatment of hyperglycemia represent major safety concerns.
- Education of hospital personnel is essential in engaging the support of those involved in the care of inpatients with hyperglycemia.
- Caution is required in interpreting results of POC glucose meters in patients with anemia, polycythemia, hypoperfusion, or use of some medications.
- Buy-in and financial support from hospital administration are required for promoting a rational systems approach to inpatient glycemic management.

IV. Cost
- Appropriate inpatient management of hyperglycemia is cost-effective.

V. Discharge planning
- Preparation for transition to the outpatient setting should begin at the time of hospital admission.
- Discharge planning, patient education, and clear communication with outpatient providers are critical for ensuring a safe and successful transition to outpatient glycemic management.

VI. Needed research
- A selected number of research questions and topics for guiding the management of inpatient hyperglycemia in various hospital settings are proposed.

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