

REVIEW

Understanding hypoglycemia in hospitalized patients



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Practice Points

- The relationship between glycemic control and mortality demonstrates a U-shaped or J-shaped curve with increased risk of death at both extremes.
- The association between hypoglycemia and mortality may be more specific to 'spontaneous hypoglycemia' as opposed to iatrogenic hypoglycemia, implying that hypoglycemia may be a biomarker for poor prognosis rather than a true cause of mortality.
- Current guidelines for inpatient glycemic control recommend maintaining blood glucose values in the range of 140–180 mg/dl (7.8–10 mmol/l) for most patients. Values <100 mg/dl (5.6 mmol/l) should be avoided, and therapy needs to be revised when values are <70 mg/dl (3.9 mmol/l).
- Hypoglycemia unawareness is common particularly in ill and elderly hospitalized patients, often having low glucose levels without symptoms. For pragmatic reasons treatment is necessary when glucose levels are <70 mg/dl (3.9 mmol/l) with or without symptoms.
- Less intensive control is appropriate for very ill or elderly patients, while more intensive control may be appropriate for healthy, stable inpatients.
- Risk factors for hypoglycemia include aggressive glycemic control, older age, recent hospitalization, terminal illness, number of comorbidities, renal failure, shock, mechanical ventilation, malignancy, hypoalbuminemia and antecedent episodes of hypoglycemia.

SUMMARY Controlling blood glucose in hospitalized patients is important as both hyperglycemia and hypoglycemia are associated with increased cost, length of stay, morbidity and mortality. A limiting factor in stringent control is the concern of iatrogenic hypoglycemia. The association of hypoglycemia with mortality has led to clinical guideline changes recommending more conservative glycemic control than had previously been suggested, with the use of patient specific approaches when appropriate. Healthier, stable patients may be managed with stricter control while the elderly and severely ill may be managed less aggressively. While the avoidance of hypoglycemia is essential in clinical

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practice, recent studies suggest that a higher mortality rate occurs in spontaneous rather than iatrogenic hypoglycemia. Therefore, inpatient hypoglycemia may be viewed more as a biomarker of disease rather than a true cause of fatality.

Controlling blood glucose has become a common inpatient concern. Recent data reports that more than 25% of all inpatient days are incurred by people with diabetes [1]. Although most patients are admitted for reasons unrelated to their diabetes, achieving proper glucose control is an essential aspect of quality inpatient medical care. Uncontrolled inpatient hyperglycemia is associated with increased risk of complications and mortality [2–8], as well as prolonged hospital stay [9]. While treatment of hyperglycemia is important, adequate control can be challenging during the short period of time that the patient is hospitalized, and treatment often results in hypoglycemia. Hypoglycemia is also associated with increased morbidity, mortality and length of hospital stay [10,11]. Thus, the relationship between dysglycemia and mortality has a U-shaped or J-shaped curve with increased risk of death at both extremes [12,13]. Clinicians must help patients navigate their hospital stay, avoiding both hyperglycemia and hypoglycemia. Often, the concern for iatrogenic hypoglycemia is a limiting factor in achieving adequate inpatient glucose control [14]. While hypoglycemia certainly can be fatal [15], only one inpatient randomized clinical trial showed increased mortality during intensive glycemic control [11]. It has been suggested that the association between low blood sugars and mortality is related to ‘spontaneous hypoglycemia’ as opposed to iatrogenic hypoglycemia – implying that hypoglycemia may be a biomarker of disease severity rather than a true cause of mortality [12,16–18]. Current inpatient guidelines suggest a patient-centered approach, whereby tighter control may be appropriate for some patients and less intensive control for severely ill or elderly patients, with the goal of avoiding the perils of both hyperglycemia as well as hypoglycemia. This article is intended to help clinicians to review the existing literature and current clinical guidelines aimed at managing inpatient hyperglycemia, while avoiding hypoglycemia.

Definitions, classifications & prevalence

Defining a single measurement threshold for hypoglycemia is complex since the physiological thresholds vary with age, gender and health status. In addition, recent hypoglycemic episodes

will lower the threshold at which patients experience symptoms in response to low blood sugar, while poorly controlled diabetics with chronic hyperglycemia may experience symptoms at higher glucose levels from relative hypoglycemia. In hospitalized patients, hypoglycemia unawareness is common and the healthcare provider should be alerted by a value of blood glucose <70 mg/dl (3.9 mmol/l). This level is pragmatic, data driven and recommended by the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), the Endocrine Society, and by the Joint British Diabetes Society and Diabetes UK [7,19]. The latter have coined a phrase, ‘make four the floor’ [10]. This value is recommended because it approximates the lower limit of normal postabsorptive plasma glucose concentration and the glycemic threshold for activation of glucose counter regulatory responses. The value is practical in that it is higher than the glycemic threshold for hypoglycemic symptoms in most patients, allowing time for caregivers to respond and prevent a more severe clinical event. It also provides some margin for the limited accuracy of glucose monitoring devices that exists at lower glucose concentrations [19,20].

As not all patients experience a correlation between symptoms and plasma glucose levels, the ADA workshop on hypoglycemia has developed a new classification of hypoglycemia that is summarized in **Box 1** [19]. This classification is useful to better define and better understand hypoglycemic events.

The prevalence and incidence of inpatient hypoglycemia varies depending upon the inpatient setting in question and the glycemic threshold used in each study. The prevalence is higher among sicker patients or those on more aggressive glycemic regimens, reported as high as 45% of patients during intensive management [11]. In outpatient populations, hypoglycemia is at least two- to three-times more prevalent in Type 1 diabetes, however given the overwhelming prevalence of Type 2 diabetes, most episodes occur in Type 2 diabetes [21,22]. Nocturnal hypoglycemia is nearly twice as common as day time episodes [23]. Using the threshold of glucose <70 mg/dl (3.9 mmol/l), the prevalence of inpatient hypoglycemia has been estimated to be 10.1% in the

intensive care unit (ICU) and 3.5% in non-ICU settings [24]. More recently the largest retrospective study of patients admitted to the general medical floors showed a prevalence of 10.5% [12]. Hypoglycemia <40 mg/dl (2.2 mmol/l) was reported at 1.9% of ICU patients and hypoglycaemia <50 mg/dl (2.8 mmol/l) was reported in 7.7% of admissions to a general medical floor [10,25]. When looking specifically at patients with Type 2 diabetes admitted to medical and surgical floors, the overall prevalence ranges from 3–29% [26–28].

Absence of hypoglycemic symptoms

The first step in preventing and treating hypoglycemia is increasing awareness among patients and caregivers regarding symptoms. The 11 most common symptoms have been used to form the Edinburgh Hypoglycemia Scale divided into autonomic, neuroglycopenic and general symptoms. Autonomic symptoms consist of sweating, palpitations, shaking and hunger. Neuroglycopenic symptoms include confusion, drowsiness, odd behavior (including aggressive behavior or seizures), speech difficulty, and in coordination. Some patients may also experience general malaise, headaches or nausea. Autonomic symptoms result from the stimulation of the sympathoadrenal system, while neuroglycopenic symptoms results from cerebral glucose deprivation [101]. In the autonomic response the increased secretion of acetylcholine leads to sweating and hunger while increased epinephrine and norepinephrine leads to palpitations and tremors. This is part of the physiologic defense against hypoglycemia and prompts the normal behavioral response of carbohydrate ingestion [29].

Many patients with diabetes and repeated episodes of hypoglycemia are unable to properly display or sense these symptoms, termed hypoglycemia unawareness or hypoglycemia associated autonomic failure (HAAF). This is particularly common in individuals with diabetes of long-term duration and can also be found in the ill or hospitalized patient. When plasma glucose levels fall, the normal physiologic response is to decrease endogenous insulin secretion and increase glucagon, at lower glucose levels epinephrine also increases in order to restore euglycemia [29]. Recurrent or recent hypoglycemia may attenuate this counter regulatory response, lowering the glucose threshold at which counter regulation is triggered. In some patients the level of glucose required to stimulate a response may

Box 1. Classification of hypoglycemia.

Severe hypoglycemia

- An event requiring assistance

Documented symptomatic hypoglycemia

- Symptoms and glucose ≤ 70 mg/dl (3.9 mmol/l)

Asymptomatic hypoglycemia

- Absence of symptoms and glucose ≤ 70 mg/dl (3.9 mmol/l)

Probably symptomatic hypoglycemia

- Symptoms without documented low glucose ≥ 70 mg/dl (3.9 mmol/l)

Pseudohypoglycemia

- Symptoms and glucose ≥ 70 mg/dl (3.9 mmol/l)

Data taken from [19].

be below the glucose level associated with neuroglycopenia and such patients will experience confusion as the first symptom of hypoglycemia. Such patients with ‘silent hypoglycemia’ are unable to alert medical attention, placing them in particular need of proper medical surveillance. The lack of proper counter regulation and the patient’s inability to sense autonomic symptoms (‘hypoglycemia unawareness’) are the two components of HAAF. Hypoglycemia unawareness itself is associated with a sixfold increased risk of future severe hypoglycemia, while HAAF is associated with a 25-fold increased risk. While HAAF is well recognized in individuals with Type 1 diabetes, particularly in those with long disease duration and significant deficiency of endogenous insulin, it is also common in Type 2 diabetes. It is, however, less recognized in hospitalized individuals particularly the elderly or the critically ill patient with organ failure and it is important that clinicians be vigilant in avoiding iatrogenic hypoglycemia in the inpatient setting [19,29]. Current research has shown that counter regulatory defects can be attenuated or reversed by selective serotonin reuptake inhibitors, adrenergic antagonists, opiate receptor antagonists, fructose and a selective ATP-sensitive potassium channel agonist [29]. The reversibility to normal counter regulation with these agents is supports the concept that HAAF is an adaptive response to hypoglycemia rather than a maladaptation.

Risk factors

Hypoglycemia can be either iatrogenic or ‘spontaneous’, and can result from underlying medical illness, even in the absence of antidiabetic agents. Inpatients, particularly the elderly, are at risk for iatrogenic hypoglycemia for a variety of reasons. These include intensive glucose management, presence of HAAF, organ

failure (e.g., chronic kidney disease, congestive heart failure and liver failure) and polypharmacy (see **Box 2**). Hypoglycemia is particularly common in patients exposed to hypoglycemic agents, such as insulin or sulfonylurea therapy. Reduced caloric intake also plays a role in patients with anorexia, nausea and/or vomiting, or when food is withheld (nothing by mouth orders). In addition, patients treated with hypoglycemic agents often have poorly coordinated meal and medication timing. A simple delay in providing a food tray can be a cause of hypoglycemia, particularly in those treated with insulin. Other potential causes may be maintenance of the same hypoglycemic agents or doses despite resolution of the underlying illness and as insulin resistance improves. For instance, a patient with pneumonia may need to be treated with high insulin doses, and may develop hypoglycemia once the pneumonia is resolved causing less insulin resistance. Also, increased mobilization after an illness or a major limb amputation can result in increased insulin sensitivity and low blood glucose levels when hypoglycemic regimens are not adjusted [12,19,25,30,101].

Certain nonhypoglycemic drugs may also precipitate hypoglycemia. The most commonly reported offending drugs are quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and IGF-1 [31]. The evidence is strongest for the association of hypoglycemia with cibenzoline, gatifloxacin, pentamidine, quinine, indomethacin and glucagon (during endoscopy) [32]. More recently ranolazine, a medication used for treatment of chronic angina among other cardiac conditions, has been shown to lower blood sugar levels and can cause hypoglycemia particularly when combined with hypoglycemic agents [33].

Important risk factors and predictors of spontaneous hypoglycemic events in hospitalized patients include increased age, recent or repeat hospitalization and/or previous hypoglycemic events. Other risk factors include terminal illness, comorbidities such as renal failure, shock, the need of mechanical ventilation, malignancy and hypoalbuminemia [12,19,25,30]. Finally, while less common, endocrine disorders causing loss of anti-insulin hormone function can pose a risk for hypoglycemia, as in adrenal insufficiency, growth hormone deficiency, hypothyroidism and hypopituitarism [101].

Complications & consequences

Hypoglycemia can lead to significant morbidity and occasional mortality, with recurrent hypoglycemia being the most common complication. This places patients at risk of more severe hypoglycemia risk with a dose-dependent response, with mortality increasing proportionally with the frequency and severity of hypoglycemia [11,12,19]. Inpatient hypoglycemia is also associated with increased cost mainly owing to increased length of stay [10,34].

Hypoglycemia can affect cognitive function in adults, although the effects are more significant in children under the age of 5 years [35]. Large data obtained in adults during the 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) showed transient cognitive dysfunction but similar performances on cognitive tests between patients with and without a history of severe hypoglycemia reassuring no permanent brain damage [36]. In hospitalized patients, short-term cognitive impairment during hypoglycemic episodes should be avoided as it can lead to trauma from falls or seizures, often extending the hospital stay [30].

A number of case reports, mostly in children, have shown that hypoglycemia can be fatal in 4–10% of patients with Type 1 diabetes [19,36–39]. In the adult population, prolonged or severe hypoglycemia can cause brain injury, but most cases of fatal hypoglycemia have been attributed to ventricular arrhythmias, the so-called ‘dead in bed syndrome’ [15].

Recent literature supports the concept that spontaneous, but not necessarily iatrogenic hypoglycemia is associated with risk of death. Among the major inpatient trials of intensive glycaemic management, only NICE-SUGAR, a large multicenter trial, reported an overall increase in mortality with intensive insulin therapy [11]. Also, in a retrospective analysis of patients with diabetes admitted to the general wards a correlation of hypoglycemia with increased mortality was found, but this association held true even at 1 year postdischarge, implying that hypoglycemia was a marker of disease burden rather than a direct cause of mortality [10]. By contrast, several studies shown in **Table 1** have demonstrated a decrease in mortality with intensive insulin control [40–42], while others failed to show any significant association, and two multicenter randomized-controlled trials (VISEP and Glucontrol) had to be terminated early owing to high rates of severe hypoglycemia,

but there was no evidence of increased mortality [43,44]. The only trials carried out in patients with diabetes are the DIGAMI trials that showed a decrease in mortality with tight glycaemic control at 1 and 5 years follow-up [45]. The DIGAMI-2 trial failed to show a long-term benefit with more aggressive insulin regimens as compared with conventional therapy [46]. For a summary of the results of inpatient trials on the association between hypoglycemia and mortality, see **Table 1**. In a meta-analysis, including the results of NICE-SUGAR, no overall benefit or harm was seen with intensive glycaemic control [16]. A *post hoc* analysis of the NICE-SUGAR trial demonstrated attenuated hazard ratios after adjustment for baseline characteristics and post-randomization factors. They also noted that the hazard ratio for death was greater (and the time to death shorter) among patients who had hypoglycemia not being treated with insulin, as compared with the patients treated with insulin [11]. These findings support the notion that spontaneous hypoglycemia, rather than iatrogenic hypoglycemia, is associated with increased mortality.

Other studies have also questioned whether hypoglycemia is truly a cause of mortality or simply a biomarker of increased disease burden and poor prognosis. One study of patients with acute myocardial infarction found that hypoglycemia (glucose <60 mg/dl or 3.3 mmol/l) was a predictor of in-hospital mortality but only in patients with spontaneous hypoglycemia, while iatrogenic hypoglycemia was not associated with increased mortality [13]. This concept was further supported by a large retrospective study of hypoglycemia (glucose <70 mg/dl or 3.9 mmol/l) in hospitalized patients, which showed that only spontaneous hypoglycemia was associated with increased mortality but not iatrogenic hypoglycemia. However, when adjusted for comorbidities, even the association of spontaneous hypoglycemia and mortality disappeared. These findings imply that in most cases, hypoglycemia is a biomarker of disease rather than a direct cause of fatality [12].

Nevertheless, trials such as NICE-SUGAR raise concern for the effects of iatrogenic hypoglycemia, leading to changes in the clinical guidelines to be discussed below. The variable results of these trials has also raised awareness of a need for glycaemic control to be tailored to patient specific situations, where younger and healthier patients may benefit from more intensive glycaemic control while older and

Box 2. Risk factors for inpatient hypoglycemia.

Medication related

- Intensive glycaemic control
- Hypoglycaemic agents
- Nonhypoglycaemic agents
- Polypharmacy

Patient characteristics

- Older age
- Short life expectancy
- Increased duration of diabetes
- Previous history of severe hypoglycemia
- Antecedent hypoglycemia
- Sleep
- Recent or frequent hospitalizations

Comorbidities

- Renal failure
- Congestive heart failure
- Hepatic failure
- Sepsis
- Malignancy
- Mechanical ventilation

Nutrition

- Low caloric intake
- Delayed or missed meals
- Lack of synchronization between meal timing and prandial insulin

sicker patients can be managed with relaxed protocol [30].

Managing inpatient hyperglycemia while avoiding hypoglycemia

Given that both hypoglycemia and hyperglycemia may pose an increased risk of inpatient morbidity and mortality, the most recent inpatient guidelines seek to provide 'practical, achievable and safe' glycaemic targets with which to treat hyperglycemia, while also fastidiously avoiding hypoglycemia. The most relevant guidelines for inpatient management are the 2009 AACE and ADA Consensus Statement on Inpatient Glycaemic Control, and the 2012 Endocrine Society Clinical Practice Guideline on Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting [7,47].

ICU recommendations

Glycaemic targets

After the NICE-SUGAR trial demonstrated an increased mortality in the intensive glycaemic control arm, the guidelines were modified to be less stringent (**Table 2**). AACE/ADA

Table 1. Intensive glycemc control studies and rates of hypoglycemia and mortality.

Study, n (% diabetes)	Glucose goal, mg/dl (mmol/l)	Rate of hypoglycemia (intensive vs comparator)	Mortality impact	Ref.
Surgical ICU, 1548 (13)	80–110 (4.4–6.1)	5 vs 0.78%	Decreased; 43% ICU, p = 0.01; 34% hospital, p = 0.01	[41]
Medical ICU, 1200 (17)	80–110 (4.4–6.1)	18.7 vs 3.1%	Decreased; 9.5%, p = 0.009 (ICU stay >3 days)	[40]
WISEP, 537 (30)	80–110 (4.4–6.1)	17 vs 4.1%	Unchanged; study terminated early	[43]
GLUCONTROL, 1101 (19)	80–110 (4.4–6.1)	8.7 vs 2.7%	Unchanged; study terminated early	[44]
NICE–SUGAR, 6104 (20)	81–108 (4.4–6.1)	6.8 vs 0.5%	Increased; 2.6%, p = 0.02 –day 90; unchanged at day 28	[11]
DIGAMI, 620 (100)	71–100 (3.9–5.6)	15 vs 0%	Decreased; 28%, p = 0.011 at 5 years	[45]
DIGAMI 2, 1253 (100)	71–100 (3.9–5.6)	12.7 vs 9.6% 12.7 vs 1.0%	Unchanged; between 3 arms	[46]

ICU: Intensive care unit.
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guidelines recommend using an insulin infusion to achieve a starting glucose threshold below 180 mg/dl (10 mmol/l) with a goal range of 140–180 mg/dl (7.8–10 mmol/l), noting that ‘greater benefit’ may be realized at the lower end of the range. Emphasizing a patient-centered approach that avoids hypoglycemia, they suggest that lower targets may be appropriate for some patients, but recommend against glucose values <110 mg/dl (6.1 mmol/l) [47]. The Endocrine Society guidelines also acknowledge that a target range of <200 mg/dl (11.1 mmol/l) may be appropriate for patients with terminal illness, limited life expectancy or increased risk of hypoglycemia [7].

Treatment strategies

Continuous intravenous insulin infusion is the most effective method of achieving glycemc targets in the ICU setting. The intravenous route allows for rapid dosing adjustments to address the frequent changes in the status of critically ill patients and help calculate the insulin needs based on the degree of insulin sensitivity [48]. This protocol is best implemented with validated computerized protocols that allow for predefined adjustments in the insulin rate based upon glycemc fluctuations [47]. When patients are clinically ready to transition to subcutaneous insulin (i.e., they begin eating or enter the general wards), that total daily insulin dose can be used for guidance in the transition to subcutaneous insulin administration. Often 75–80% of the total daily intravenous infusion dose administered can be divided into basal and prandial components. This transition should ideally be carried out in a proactive manner by administering

subcutaneous insulin 1–4 h before the intravenous infusion is discontinued, depending upon the type of subcutaneous insulin given [7,47,49]. When dividing the basal and prandial components, patients with a restricted caloric intake are recommended to receive 60–80% of the total daily dose as basal insulin. Patients with a stable caloric intake should receive their daily insulin dosage as an equal combination of approximately 50% basal and 50% bolus insulin. The bolus or prandial insulin is provided as three injections with meals that have consistent carbohydrates [47,50]. Patients receiving an intravenous insulin infusion rate of 1 U/h or less may not require a scheduled subcutaneous regimen, but still need to be carefully monitored [47]. It is essential to be proactive and have a plan that invariably will need to be adjusted according to the regimen provided and glycemc response.

■ **General wards recommendations**

Glycemc targets

As no prospective randomized control trial to date specifically addresses non-ICU patients, guidelines for noncritically ill patients are based upon retrospective data and expert clinical experience. For most patients admitted to the general wards, current guidelines advise glycemc goals of premeal glucose <140 mg/dl (7.8 mmol/l) and a random glucose <180 mg/dl (10 mmol/l). The medication regimen should be reassessed if a glucose level declines below 100 mg/dl (5.6 mmol/l) and modified when values are <70 mg/dl (3.9 mmol/l). Both guidelines stress using a patient-centered approach, allowing for stricter control in clinically stable patients with a history of good outpatient glycemc control and

looser targets in patients who are terminally ill or with severe comorbidities [7,47].

Treatment strategies

Subcutaneous insulin is the preferred method for maintaining glycemic control in non-ICU settings. Both the AACE/ADA and Endocrine Society guidelines recommend using basal insulin once or twice daily and prandial (bolus) rapid acting insulin before meals when patients are stable and eating. In choosing a basal/bolus regimen, a multicenter study comparing long-acting detemir plus rapid acting aspart to NPH plus regular insulin in Type 2 diabetics showed no difference in the level of glycemic control or frequency of hypoglycemia [26]. Both guidelines recommend against the prolonged use of sliding scale insulin therapy alone as it is ineffective in most patients and potentially dangerous in Type 1 diabetics. 'Corrective insulin' should be distinguished from sliding scale insulin in that it is customized to match a patient's insulin sensitivity and should take into account timing of food and pre-existing insulin administration. More importantly, corrective insulin is intended to be a supplement to a basal regimen, not a standalone regimen as sliding scales are sometimes implemented [7,47]. Sliding scales are inherently a reactive approach that is lacking in data, not based in physiology and leads to more hyperglycemia and hypoglycemia. Basal regimens are more proactive and less prone to blood glucose variability [51].

Oral agents

Oral agents should be discontinued for most hospitalized patients since there are frequent contraindications to their use. Sulfonylureas often are not effective, and when effective may cause prolonged hypoglycemia especially in the elderly, renally impaired and/or in those with poor nutritional intake. The risk of hypoglycemia is

similar with shorter acting secretagogues such as repaglinide and nateglinide. Metformin should also be held as hospitalized patients are at risk of developing renal insults, such as from diagnostic tests using contrast dye or surgery, and should be discontinued in the setting of decompensated heart failure, renal insufficiency, hypoperfusion or chronic pulmonary disease. The possibility of lactic acidosis while rare may occur in those with renal failure. Thiazolidinediones may take several weeks for the full effect, limiting their usefulness in inpatient glycemic control and are also contraindicated in congestive heart failure or hepatic dysfunction [7,47,52]. The use of incretins such as oral dipeptidyl peptidase intravenous inhibitors and injectable glucagon-like peptide-1 agonists is now being considered. The incidence of hypoglycemia is low with incretin agents when used without other hypoglycemic agents, and while injectables can be challenging owing to dose titration and gastrointestinal side effects, the use of these agents alone or in combination with basal insulin has been advocated and may become more common [53]. Certainly larger randomized controlled trials are needed to evaluate the use of incretins for inpatient diabetes management [54]. Under the current guidelines, oral agents, while not generally recommended, may on occasion be appropriate for specific patients who are stable, expected to eat regular meals and have a short hospital stay [7,47]. Patients who were taking oral medications at home can be safely converted to basal insulin or basal bolus insulin based upon point of care (POC) blood glucose while in the hospital. Patients with glucose >140 mg/dl (7.8 mmol/l) can be treated with basal or basal-bolus insulin dosing based upon their bodyweight, although patients who are non per os (NPO) should only receive basal insulin with regularly scheduled correction doses of short acting or regular insulin every 4 or 6 h, respectively [7,27,28,47].

Table 2. Glycemic targets in hospitalized patients.

	2004 (ACE)	2004 (ADA)	2009 (ADA and ACE)
Intensive care units			
Glucose (mg/dl)	110	110	140–180
Glucose (mmol/l)	6.1	6.1	7.8–10
Nonintensive care units			
Preprandial glucose, mg/dl (mmol/l)	110 (6.1)	110 (6.1)	≤140 (7.8)
Postprandial glucose, mg/dl (mmol/l)	≤180 (10)	≤180 (10)	≤180 (10)
ACE: American College of Endocrinology; ADA: American Diabetes Association. Data taken from [47,59,60].			

Monitoring

The existing guidelines recommend following schedules for POC bedside glucose testing in patients with elevated blood sugar with or without diabetes. Individuals who are eating should have testing before meals and at bedtime. Pre-meal testing should be performed as close to the mealtime as possible. Patients who are receiving continuous enteral feeds or are NPO should be monitored every 4–6 h. Those who are receiving intravenous insulin infusions require more frequent monitoring, ranging from every 30 min to every 2 h. Patients with medication changes that affect glycemic control (i.e., corticosteroids), or those with abrupt changes in diet or frequent episodes of hypoglycemia should be closely monitored [7,47].

The POC testing should be performed with glucometers which meet the US FDA guidelines for accuracy (within 20% error) and some have challenged whether this level of error is acceptable [55]. Especially relevant for inpatients, capillary glucose values can vary between meters and at high or low hemoglobin levels or low tissue perfusion. Central laboratory glucose analysis must be within 10% accuracy so there may be some inconsistency between POC and central laboratory monitoring [7,47]. Hospitals need to develop and implement protocols for the proper calibration and maintenance of the monitors as well as educational programs for proficiency and certification of the personnel responsible for POC testing.

Nutrition

Nutritional concerns present some of the most difficult obstacles to proper inpatient glycemic control. Dietary changes are less important while the patient is in the hospital, and healthier diets should be pursued when out of the hospital. Avoiding caloric restriction is necessary in hospitalized individuals who are often in a catabolic state. Meals should be provided with consistent carbohydrate quantities to match prandial insulin regimens. Coordinating doses of rapid- or short-acting insulin with meal timing requires that hospital infrastructure enables communication between dietary and nursing services. Unfortunately, many hospitals are challenged by incoordination of meals with insulin regimens and inconsistent carbohydrate content of meals [7,47]. When using regular insulin, a 20–30 min wait is preferred between the insulin administration and the meal. For these reasons we prefer the use of rapid-acting

insulins, provided that they are administered just before or immediately with the meal.

Systems improvement

Both guidelines recommend that hospitals create an interdisciplinary steering committee led by local diabetes experts to assist in establishing and implementing inpatient glycemic goals. These committees offer the opportunity to create protocols and order sets to assist in treatment of both hyperglycemia and hypoglycemia that is suitable to the patient population they serve. The implementation of these programs needs to be performed in a cost-effective manner, as frequent monitoring and intensive insulin therapy in the hospital setting is expensive. Tracking frequency of hypoglycemic events with root cause analysis is ideal and should be carried out whenever possible to assist in identifying common causes and preventing future hypoglycemic events [7,47].

■ Treating hypoglycemia

The treatment of hypoglycemia is conceptually simple but requires efficient and effective coordination between hospital staff, including physicians, nurses and support staff. The Joint British Diabetes Society and Diabetes UK have recently published guidelines on ‘Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus,’ designed to be nurse led, but with many statements of prudent advice for all caregivers [101]. A nurse driven hypoglycemia treatment protocol is also recommended by the most recent guideline from the ADA/AACE as well as the Endocrine Society [7,47].

Recognition & response

Inpatient recognition of hypoglycemia can be challenging as many are asymptomatic. Therefore, frequent monitoring is essential in critically ill patients. Nurses should be encouraged to check POC blood glucose whenever a mental status change is noted, in addition to the scheduled orders, a practice that is policy in many institutions. The response to hypoglycemia requires an immediate or ‘rapid response’ based upon the hospital’s protocol. As mentioned above, a universal alert standard to define hypoglycemia that should prompt a clinical response is an essential part of treatment. Blood glucose <70 mg/dl or 3.9 mmol/l are used in most guidelines. In hospitalized patients treatment is necessary even without symptoms when blood glucose is <70 [7,101].

Treatment (rule of 15)

Patients experiencing hypoglycemia who are able to swallow should be given 15 g of rapidly absorbed carbohydrate such as 150–200 ml (4–6 ounces) of pure fruit juice or ‘regular’ soda or 8 ounces of skim milk. Alternatively 5–7 glucose tablets or 3–4 teaspoons of sugar dissolved in water may be used. POC glucose measurements should be repeated 15 min after ingestion and treatment repeated until the glucose is >80 mg/dl (4.4 mmol/l). This response should be nurse driven for efficiency but a physician should be contacted if a proper response is not obtained after three doses. Patient who are NPO, unable to swallow or unconscious should be given intravenous infusions of dextrose if intravenous access is available [7,101]. A total of 25 ml of 50% dextrose or glucose is recommended and dextrose 5% in water at 100 ml/h should be followed [7]. The use of 10 or 20% glucose infusions are also efficacious, while having less risk of extravasation injury. When access is not available, glucagon 1 mg intramuscularly should be administered [20,56,57]. Persons with poorly controlled blood glucose who experience the symptoms of hypoglycemia at glucose levels above this alert value (‘pseudohypoglycemia’) are recommended to receive a small snack such as a banana or slice of bread to avoid inducing hyperglycemia [7,101]. Baker *et al.* suggested the use of ‘hypo boxes’, brightly colored boxes placed in prominent locations that contain all equipment needed to treat hypoglycemia from juice to intravenous lines and dextrose preparations [58]. As each institution will have different resources and vary in the type of response, it is important for the nurses to be familiar with individual protocols, and where to quickly find fruit juice, soda, glucagon and dextrose solutions. The physician should analyze the precipitating factor, review and modify orders specific to the patient, knowing that one episode of hypoglycemia predisposes to further episodes of hypoglycemia.

Conclusion

Hypoglycemia is common in hospitalized patients with and without diabetes and is associated with significant morbidity and mortality. Iatrogenic hypoglycemia is a frequent cause of hypoglycemia and should be avoided. Recent guidelines advocate for more relaxed inpatient glycemic targets based on clinical trials that have failed to replicate improved outcomes in those with blood sugars that are close to normal.

Since elderly and chronically ill patients are at increased risk of hypoglycemia, they should be treated for their underlying disease while being less stringent regarding strict glycemic control. Recent evidence that spontaneous hypoglycemia, but not iatrogenic hypoglycemia, is associated with increased risk of death provides reassurance that a more aggressive approach may be beneficial for some patients, particularly younger patients or those with less comorbidities. These findings suggest that a more patient-centered approach is beneficial to target populations that need more aggressive strategies. It is important to stress that inpatient hypoglycemia is a biomarker of disease burden rather than a true cause of mortality. Regardless of the cause, clinicians need to be aware of high-risk patients who require careful monitoring and less stringent glycemic control. When a hypoglycemic event does occur, it should be treated promptly and with appropriate changes in the treatment regimen to avoid recurrent episodes.

Future perspective

Insulin therapy has long been the mainstay of therapy during acute illness, from the use of glucose, insulin and potassium solutions during myocardial infarction in the 1950s, to the early 21st century showing improved survival in those treated with intensive insulin therapy. However, subsequent trials failed to replicate similar benefits and when a large multicenter (NICE-SUGAR) trial showed an increased mortality rate with tight glycemic control, the guidelines were modified, recommending less stringent control. Hypoglycemia has remained a limiting factor in the management of hyperglycemia, and has been attributed to be the cause of death. Recent studies indicate that spontaneous rather than iatrogenic hypoglycemia is associated with a higher mortality rate, implying that hypoglycemia is just a biomarker and not a cause of death. Thus, the true benefit of tight glycemic control and the relationship between hypoglycemia and mortality leaves many unanswered questions:

- Why has intensive glycemic control produced such different outcomes? Is it differences in the protocol design, the patient populations or differences in glycemic targets?
- If spontaneous hypoglycemia has a higher mortality rate than iatrogenic hypoglycemia, is insulin therapy just ‘uncovering’ a more susceptible population with a poor prognosis?

- As patients vary widely in their health status and life expectancy, should treatment be patient centered rather than a ‘one size fits all’ approach?
- Most studies were carried out in individuals with acute illness without diabetes, while only two studies (DIGAMI and DIGAMI 2) have addressed glycemic control in patients with diabetes. More robust trials are needed to address the growing population with diabetes.
- The true incidence of hypoglycemia remains in question. With better technology now available, we should be able to achieve better glucose monitoring and provide better-designed protocols.
- Availability of newer medications such as incretins may provide better outcomes than

insulin therapy alone, and comparative trials are in order.

More research is necessary on cost-effective strategies for the management of inpatient hyperglycemia, as glycemic control, regardless of how strict, can be extremely costly.

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References

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

- 1 American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 36(4), 1033–1046 (2013).
- 2 Baker EH, Janaway CH, Philips BJ *et al.* Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 61(4), 284–289 (2006).
- 3 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355(9206), 773–778 (2000).
- 4 Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke J. Cerebral. Circ.* 32(10), 2426–2432 (2001).
- 5 Kosiborod M, Rathore SS, Inzucchi SE *et al.* Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 111(23), 3078–3086 (2005).
- 6 Krinsley JS. Association between hyperglycemia and increased hospital

mortality in a heterogeneous population of critically ill patients. *Mayo Clin. Proc. Mayo Clin.* 78(12), 1471–1478 (2003).

7 Umpierrez GE, Hellman R, Korytkowski MT *et al.* Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 97(1), 16–38 (2012).

■ ■ **Most recent clinical practice guidelines from the Endocrine Society on treatment of inpatient hyperglycemia in nonintensive care unit patients. Provides evidence-based recommendations on glycemic targets and monitoring, along with descriptions of protocols and system improvements required to facilitate these goals.**

8 Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J. Clin. Endocrinol. Metab.* 87(3), 978–982 (2002).

9 Williams LS, Rotich J, Qi R *et al.* Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 59(1), 67–71 (2002).

10 Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 32(7), 1153–1157 (2009).

■ **Retrospective cohort study of patients with diabetes hospitalized in general wards showed that hypoglycemia (<50 mg/dl or 2.8 mmol/l) was associated with increased length of stay, and higher mortality both during admission and within 1 year of discharge.**

11 Finfer S, Liu B, Chittock DR *et al.* Hypoglycemia and risk of death in critically ill patients. *N. Engl. J. Med.* 367(12), 1108–1118 (2012).

■ ■ **Large multicenter randomized controlled trial that reported an overall increase in mortality in critically ill patients treated with intensive insulin therapy versus standard therapy. Results from this trial were influential in leading to recent guideline changes that emphasize less intensive glycemic targets for inpatients.**

12 Boucai L, Southern WN, Zonszein J. Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. *Am. J. Med.* 124(11), 1028–1035 (2011).

■ ■ **Large retrospective cohort study of the relationship between inpatient hypoglycemia and mortality. Demonstrated that spontaneous hypoglycemia, but not iatrogenic, hypoglycemia is associated with an increase in mortality.**

13 Kosiborod M, Inzucchi SE, Goyal A *et al.* Relationship between spontaneous and iatrogenic hypoglycemia and mortality in

- patients hospitalized with acute myocardial infarction. *JAMA* 301(15), 1556–1564 (2009).
- 14 Cook CB, Jameson KA, Hartsell ZC *et al.* Beliefs about hospital diabetes and perceived barriers to glucose management among inpatient midlevel practitioners. *Diabetes Educ.* 34(1), 75–83 (2008).
 - 15 Cryer PE. Death during intensive glycemic therapy of diabetes: mechanisms and implications. *Am. J. Med.* 124(11), 993–996 (2011).
 - 16 Griesdale DE, De Souza RJ, van Dam RM *et al.* Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 180(8), 821–827 (2009).
 - **Meta-analysis of the current data on glycemic control and mortality in critically ill patients. Showed no overall difference in mortality between intensive or standard insulin therapies despite significantly higher risk of hypoglycemia in those treated with intensive therapy.**
 - 17 Murad MH, Coburn JA, Coto-Yglesias F *et al.* Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* 97(1), 49–58 (2012).
 - 18 Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 300(8), 933–944 (2008).
 - 19 Seaquist ER, Anderson J, Childs B *et al.* Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 36(5), 1384–1395 (2013).
 - **Most recent scientific review statement by the American Diabetes Association and the Endocrine Society of Hypoglycemia on Diabetes. Article reviews definitions, short- and long-term outcomes, impact on various patient subgroups and outpatient strategies for prevention.**
 - 20 Cryer PE. Preventing hypoglycaemia: what is the appropriate glucose alert value? *Diabetologia* 52(1), 35–37 (2009).
 - 21 Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes* 57(12), 3169–3176 (2008).
 - 22 Donnelly LA, Morris AD, Frier BM *et al.* Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet. Med.* 22(6), 749–755 (2005).
 - 23 Amiel SA. Hypoglycemia at night: a cause for alarm? *Diabetes Technol. Ther.* 14(2), 99–100 (2012).
 - 24 Cook CB, Kongable GL, Potter DJ, Abad VJ, Leija DE, Anderson M. Inpatient glucose control: a glycemic survey of 126 U.S. hospitals. *J. Hosp. Med.* 4(9), E7–E14 (2009).
 - 25 Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit. Care Med.* 35(10), 2262–2267 (2007).
 - 26 Umpierrez GE, Hor T, Smiley D *et al.* Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 94(2), 564–569 (2009).
 - 27 Umpierrez GE, Smiley D, Jacobs S *et al.* Randomized study of basal-bolus insulin therapy in the inpatient management of patients with Type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 34(2), 256–261 (2011).
 - 28 Umpierrez GE, Smiley D, Zisman A *et al.* Randomized study of basal-bolus insulin therapy in the inpatient management of patients with Type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 30(9), 2181–2186 (2007).
 - 29 Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N. Engl. J. Med.* 369(4), 362–372 (2013).
 - 30 Carey M, Boucai L, Zonszein J. Impact of hypoglycemia in hospitalized patients. *Curr. Diab. Rep.* 13(1), 107–113 (2013).
 - 31 Murad MH, Coto-Yglesias F, Wang AT *et al.* Clinical review: drug-induced hypoglycemia: a systematic review. *J. Clin. Endocrinol. Metab.* 94(3), 741–745 (2009).
 - 32 Cryer PE, Axelrod L, Grossman AB *et al.* Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice guideline. *J. Clin. Endocrinol. Metab.* 94(3), 709–728 (2009).
 - 33 Chisholm JW, Goldfine AB, Dhalla AK *et al.* Effect of ranolazine on A1C and glucose levels in hyperglycemic patients with non-ST elevation acute coronary syndrome. *Diabetes Care* 33(6), 1163–1168 (2010).
 - 34 Curkendall SM, Natoli JL, Alexander CM, Nathanson BH, Haidar T, Dubois RW. Economic and clinical impact of inpatient diabetic hypoglycemia. *Endocr. Pract.* 15(4), 302–312 (2009).
 - 35 Perantie DC, Lim A, Wu J *et al.* Effects of prior hypoglycemia and hyperglycemia on cognition in children with Type 1 diabetes mellitus. *Pediatr. Diabetes* 9(2), 87–95 (2008).
 - 36 Jacobson AM, Musen G, Ryan CM *et al.* Long-term effect of diabetes and its treatment on cognitive function. *N. Engl. J. Med.* 356(18), 1842–1852 (2007).
 - 37 Feltbower RG, Bodansky HJ, Patterson CC *et al.* Acute complications and drug misuse are important causes of death for children and young adults with Type 1 diabetes: results from the Yorkshire Register of diabetes in children and young adults. *Diabetes Care* 31(5), 922–926 (2008).
 - 38 Patterson CC, Dahlquist G, Harjutsalo V *et al.* Early mortality in EURODIAB population-based cohorts of Type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 50(12), 2439–2442 (2007).
 - 39 Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset Type 1 diabetic patients in Norway. *Diabetologia* 49(2), 298–305 (2006).
 - 40 van den Berghe G, Wilmer A, Hermans G *et al.* Intensive insulin therapy in the medical ICU. *N. Engl. J. Med.* 354(5), 449–461 (2006).
 - 41 van den Berghe G, Wouters P, Weekers F *et al.* Intensive insulin therapy in critically ill patients. *N. Engl. J. Med.* 345(19), 1359–1367 (2001).
 - 42 Vlasselaers D, Milants I, Desmet L *et al.* Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 373(9663), 547–556 (2009).
 - 43 Brunkhorst FM, Engel C, Bloos F *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N. Engl. J. Med.* 358(2), 125–139 (2008).
 - 44 Preiser JC, Devos P, Ruiz-Santana S *et al.* A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med.* 35(10), 1738–1748 (2009).
 - 45 Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 314(7093), 1512–1515 (1997).
 - 46 Malmberg K, Ryden L, Wedel H *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J.* 26(7), 650–661 (2005).
 - 47 Moghissi ES, Korytkowski MT, Dinardo M *et al.* American Association of Clinical Endocrinologists and American Diabetes

- Association consensus statement on inpatient glycemic control. *Endocr. Pract.* 15(4), 353–369 (2009).
- **Most recent consensus statement by the American Association of Clinical Endocrinologists and the American Diabetes Association on inpatient glycemia control. Provides evidence-based recommendations for both critically ill and noncritically ill patients regarding glycemic targets, treatment options, glucose monitoring, and systems improvements required to achieve these goals.**
 - 48 Clement S, Braithwaite SS, Magee MF *et al.* Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 27(2), 553–591 (2004).
 - 49 Noschese M, Donihi AC, Koerbel G *et al.* Effect of a diabetes order set on glycaemic management and control in the hospital. *Qual. Saf. Health Care* 17(6), 464–468 (2008).
 - 50 Schmeltz LR, Desantis AJ, Schmidt K *et al.* Conversion of intravenous insulin infusions to subcutaneously administered insulin glargine in patients with hyperglycemia. *Endocr. Pract.* 12(6), 641–650 (2006).
 - 51 Browning LA, Dumo P. Sliding-scale insulin: an antiquated approach to glycemic control in hospitalized patients. *Am. J. Health Syst. Pharm.* 61(15), 1611–1614 (2004).
 - 52 Calabrese AT, Coley KC, Dapos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch. Intern. Med.* 162(4), 434–437 (2002).
 - 53 Schwartz S, Defronzo RA. Is incretin-based therapy ready for the care of hospitalized ill patients with Type 2 diabetes?: The time has come for GLP-1 receptor agonists! *Diabetes Care* 36(7), 2107–2111 (2013).
 - 54 Umpierrez GE, Korytkowski M. Is incretin-based therapy ready for the care of hospitalized patients with Type 2 diabetes? Insulin therapy has proven itself and is considered the mainstay of treatment. *Diabetes Care* 36(7), 2112–2117 (2013).
 - 55 Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? *Clin. Chem.* 55(1), 18–20 (2009).
 - 56 Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. *Emerg. Med. J.* 22(7), 512–515 (2005).
 - 57 Wood SP. Is D50 too much of a good thing? A reappraisal of the safety of 50% dextrose administration in patients with hypoglycemia. *JEMS* 32(3), 103–106, 108, 110 (2007).
 - 58 Baker H, Hammersley M, Stephenson S, Sumner J. Managing hypoglycaemia in hospital. *J. Diabetes Nurs.* 11(3), 108–111 (2007).
 - 59 American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 28(Suppl. 1), S4–S36 (2005).
 - 60 Garber AJ, Moghissi ES, Bransome ED *et al.* American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr. Pract.* 10(Suppl. 2), 4–9 (2004).

■ Website

- 101 Stanistreet D, Walden E, Jones C, Graveling A. The hospital management of hypoglycaemia in adults with diabetes mellitus. Guidelines developed by joint British Diabetes Society and Diabetes UK (Revised September 2013). www.diabetologists-abcd.org.uk/subsite/JBDS_IP_Hypo_Adults_Revised.pdf

- **Recent inpatient guideline statement on management of hypoglycemia led by the Joint British Diabetes Society and Diabetes UK. Discusses risk factors, causes, management and treatment of hypoglycemia.**