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HOSPITAL MANAGEMENT OF DIABETES (G UMPIERREZ, SECTION EDITOR)

Inpatient Hypoglycemia: A Challenge That Must Be Addressed

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Abstract Hypoglycemia in the inpatient setting is a common occurrence with potentially harmful outcomes. Large trials in both the inpatient and outpatient settings have found a correlation between hypoglycemia and morbidity and mortality. The incidence of hypoglycemia is difficult to assess, due to a lack of standardized definitions and different methods of data collection between hospital systems. Risk factors that predispose to hypoglycemia involve the changing clinical statuses of patients, nutrition issues, and hospital processes. Mechanisms contributing to morbidity due to hypoglycemia may include an increase in sympathoadrenal responses, as well as indirect changes affecting cytokine production, coagulation, fibrinolysis, and endothelial function. Prevention of hypoglycemia requires implementation of several strategies that include patient safety, quality control, multidisciplinary communication, and transitions of care. In this article, we discuss all of these issues and provide suggestions to help predict and prevent hypoglycemic episodes during an inpatient stay. We address the issues that occur upon admission, during the hospital stay, and around the time of discharge. We believe that decreasing the incidence of inpatient hypoglycemia will both decrease costs and improve patient outcomes.

Keywords Inpatient · Hypoglycemia · Diabetes · Complications · Prevention · Insulin

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Introduction

Hypoglycemia is an undesirable side effect of intensive therapy and has potentially detrimental consequences. This is even more relevant in the inpatient setting when there are constant acute changes in the patients' health status, diet, and medication regimen. The reasons behind the frequency and severity of hypoglycemia in the inpatient setting are numerous. We discuss these factors in detail in this review. Initially, in the early 2000s, the prevailing thought was that inpatient blood sugars needed to be tightly controlled, since this would reduce mortality, morbidity, and infections. This opinion was formed taking into consideration the initial studies from Van den Berghe (2001). A large number of studies during the last decade have now illustrated that although inpatient hyperglycemia is detrimental, controlling it without regard to hypoglycemia can negate the benefits of treating hyperglycemia. We discuss this in detail. Lastly, in recent years, there have been a large number of studies that illustrate the usefulness of system-wide approaches to prevent hypoglycemia in the inpatient setting. These also are discussed.

Incidence

The incidence of inpatient hypoglycemia has been reported to range from 0.5 % to 32.8 % of patients [1–4, 5••, 6, 7, 8•, 9, 10]. The true incidence can be challenging to accurately assess and compare between data sets, because of a number of factors. First, there are no standardized definitions of hypoglycemia, which makes data analysis challenging. Some studies define hypoglycemia as glucose values of ≤40 mg/dl, such as NICE-SUGAR, VISEP, and GLUCONTROL [5••, 6, 7]. Others report "severe hypoglycemia" not on the basis of a number, but as an episode of low blood glucose requiring assistance from another person, such as the ACCORD trial

[11]. ADA guidelines define hypoglycemia as any blood glucose level of <70 mg/dl [12••], which correlates with the threshold for the release of counterregulatory hormones. There is no consensus on the definition of severe hypoglycemia, but it is usually defined as a blood glucose level of <40 mg/dl [13].

Different methods of data collection, such as bedside point-of-care glucose versus plasma glucose with or without symptoms of hypoglycemia, make comparisons between different data sets challenging. Additionally, patients with hypoglycemia unawareness, combined with an inadequate frequency of glucose monitoring in the inpatient setting, can lead to an underestimation in rates of hypoglycemia. Data from continuous glucose monitoring show that hypoglycemic events are underreported by self-monitoring and are often clinically silent [3].

Risk Factors for Inpatient Hypoglycemia

There are numerous risk factors for inpatient hypoglycemia, and these can be broadly divided into patient factors, nutrition factors, and systemic factors. When Elliott et al. analyzed data on 172 patients who had experienced severe inpatient hypoglycemia (blood glucose <40 mg/dl), they found that the most common causes for these events included inadequate monitoring of blood glucose trends, changes in nutritional status without changes in diabetes treatment, excessive insulin doses, nursing administration errors, and insufficient glucose with insulin for the acute treatment of hyperkalemia [3].

Patient Factors

Since underlying illnesses can lead to variability in insulin sensitivity, it is extrapolated that the risk of hypoglycemia is potentially higher in the inpatient setting, as compared with the outpatient setting [14]. The most common clinical status changes increasing the risk of hypoglycemia include acute kidney injury [3, 15] and evolving sepsis [2]. Stopping or starting medications such as beta-adrenergic agonists, quinolone antibiotics, vasopressors, and corticosteroids can cause both hypoglycemia and hyperglycemia [13, 16]. Continuing long-acting sulfonylureas in the hospital can cause hypoglycemia, especially in elderly patients with renal or hepatic insufficiency [13]. Irrespective of events surrounding their hospitalization, patients with an increased duration of diabetes, low BMI, malnutrition, hemoglobin A1c <7 %, previous cardiovascular events, insulin treatment at baseline, advanced age, and a higher albumin-to-creatinine ratio all have an increased risk of hypoglycemia [2, 3, 15, 17]. In general, there is less risk of hypoglycemia in type 2 diabetes, as compared with type 1 diabetes, but the frequency of hypoglycemia can increase with an increased duration of diabetes and treatment with insulin [18•].

Nutrition Factors

Nutrition factors that can increase the possibility of hypoglycemia include (1) erratic oral intake, (2) missing meals, and (3) lack of coordination between meal delivery, blood glucose monitoring, and prandial insulin administration [3, 16, 19]. Hypoglycemia can often occur in patients receiving a fixed dose of mealtime insulin despite the fact that their oral intake is diminished while they are inpatients. Patients who are on enteral tube feeds or parenteral nutrition and have hyperglycemia often require long-acting insulin to attain goal blood glucose levels. However, they can also develop hypoglycemia if feedings are interrupted and insulin is not appropriately adjusted or the glucose content from feedings is not replaced [20]. In our experience, this most frequently happens when feedings are held prior to procedures, for elevated gastric residuals, or if intravenous or enteral access is lost.

Systemic Factors

Errors related to hospital processes and communication errors among members of a patient's care team can be the most difficult to identify and, subsequently, correct. Hospitalized patients with diabetes have an increased incidence of medical errors, experiencing >0.53 errors per patient days and >1.72 errors per patient period [3, 13].

Differing levels of knowledge and training of staff, poor communication during the transitions of care between different teams, and a lack of standardized protocols or order sets all predispose patients to hypoglycemia [13, 16, 21, 22]. Prolonged use of sliding scale insulin as monotherapy can also lead to hypoglycemia [23]. Antecedent mild hypoglycemia was seen prior to a severe hypoglycemic event in over 60 % of severe events analyzed by Elliott et al., indicating that failing to make changes to glycemic therapy on the basis of daily blood glucose patterns is a common occurrence [3].

There can be a lack of ownership for inpatient diabetes management, particularly in settings where the primary diagnosis is unrelated to diabetes and patients are admitted to more specialized services [19]. When patients experience hypoglycemia while on enteral tube feeds or parenteral nutrition, it is often more common when the same providers are not directing both nutrition and insulin administration. In this situation, communication is essential between physicians and nursing staff. If communication is lacking, this can increase the risk of errors and delay necessary treatment changes [13]. An increase in insulin is often needed when patients receive steroids in the hospital, and reduction of steroids usually requires an additional coordinated adjustment of

insulin. If this concurrent taper does not occur, this can lead to hypoglycemia [24, 25].

Hypoglycemia can also be the result of preventable errors. Errors in order writing or orders that are unclear or complicated can contribute to inpatient hypoglycemia [26]. Errors in insulin administration can also be a major of hypoglycemia [27]. While insulin is designated as a high-risk medication, the true frequency of inpatient insulin errors is unknown, primarily because the availability of data depends on voluntary reporting of errors [28]. Additionally, most hospitals do not have the mechanisms for root-cause analysis available [13].

Hypoglycemia in Patients Without Diabetes or Hyperglycemia

In most people, the cause of hypoglycemia in the hospital is a consequence of treatment of hyperglycemia. However, there are some conditions that predispose patients to developing hypoglycemia that are unrelated to the treatment of hyperglycemia. A study from Kosiborod et al. in 2009 looked at whether inpatient hypoglycemia is directly related to adverse events or is, instead, indicative of a greater severity of illness [29]. They studied nearly 8,000 patients hospitalized with acute myocardial infarction, looking at the prognostic implications of hypoglycemia in patients who developed hypoglycemia spontaneously, as compared with those who experienced it after receiving insulin [29]. While patients with spontaneous hypoglycemia had significantly higher rates of in-hospital mortality than those without hypoglycemia (18.4 % vs. 9.2 %), mortality rates were not increased in patients with hypoglycemia that were being treated with insulin (10.4 % vs. 10.2 % in patients without hypoglycemia). A later study in 2011 by Boucai et al. looked at the mortality risk of hypoglycemia using a retrospective cohort of over 31,000 patients admitted to a general medicine ward. Of the patients reviewed, 10.5 % had at least one episode of hypoglycemia. While hypoglycemia was associated with increased in-hospital mortality, the risk was limited to patients with spontaneous hypoglycemia, not to patients with drug-associated hypoglycemia. Additionally, after adjusting for patient comorbidities, no association was found between spontaneous hypoglycemia and mortality [30]. These findings suggest that inpatient hypoglycemia may be a marker of illness severity, instead of a cause of an adverse event [20, 29, 30].

Consequences of Inpatient Hypoglycemia

Large trials in both the inpatient and outpatient setting have found a correlation between hypoglycemia and increased morbidity and mortality [5••, 7]. Both outpatient and inpatient studies have reported varying results regarding morbidity and mortality (Table 1) [4, 11, 17]. We will focus our subsequent discussion on these studies.

Initial enthusiasm for tight glucose control in the inpatient setting was sparked by a 2001 study by Van Den Berghe et al., which showed that intensive insulin therapy to maintain blood glucose at or below 110 mg/dl reduced mortality from 8 % to 4.6 % among critically ill patients in the surgical intensive care unit (ICU) [31]. Reported rates of hypoglycemia (defined as blood glucose of ≤40 mg/dl) were unusually low at 1.9 % in the conventional and 5.2 % in the intensively treated groups [31].

The VISEP trial looked at 537 patients with severe sepsis receiving either intensive insulin therapy (goal blood glucose of 80–110 mg/dl) or conventional insulin therapy (goal blood glucose of 180–200 mg/dl) and was stopped early due to safety reasons [6]. Rates of severe hypoglycemia (defined as blood glucose of ≤40 mg/dl) were higher in the intensive-therapy group than in the conventional-therapy group (17 % vs. 4.1 %), and there was a trend toward a prolonged stay in the ICU. No difference in mortality was noted between the two groups [6].

The NICE-SUGAR trial studied over 6,000 ICU patients receiving either intensive glucose control (target blood glucose of 81–108 mg/dl) or conventional glucose control (target blood glucose of 180 mg/dl or less) [5••]. They found that intensive glucose control increased mortality by 2.6 %. Severe hypoglycemia (defined as blood glucose ≤40 mg/dl) was more common in the intensive control group (6.8 % vs. 0.5 %), suggesting a link between hypoglycemia and mortality [5••].

The GLUCONTROL study looked at 1,101 patients admitted to 21 ICUs, randomized to two groups, one with a target blood glucose of 140–180 mg/dl, the other with a target of 80–110 mg/dl [7]. Rates of hypoglycemia (defined as blood glucose ≤40 mg/dl) were higher in the more intensive group (8.7 % vs. 2.7 %), but ICU mortality was similar in both, thus showing a lack of clinical benefit in intensive insulin therapy. Of note, patients in both groups who experienced hypoglycemia had higher mortality rates [7].

Mechanisms Contributing to Morbidity and Mortality Associated with Hypoglycemia

A number of mechanisms could contribute to hypoglycemia causing adverse cardiovascular outcomes. Hypoglycemia induces a number of counterregulatory responses, which together likely contribute to increased morbidity and mortality [32–34]. Pancreatic beta cell insulin secretion is decreased, whereas pancreatic alpha cell secretion of glucagon is increased during an episode of hypoglycemia [32–34]. An increased sympathoadrenal response results in acute plasma increase in epinephrine and norepinephrine, as well as increased levels of ACTH and cortisol [32–34]. This increase in catecholamines causes increased myocardial contractility, myocardial workload, and cardiac output [35]. In patients with

Table 1 Major studies of diabetes and hypoglycemia

Trial Name	Population	Definition of Hypoglycemia	Hypoglycemia in Intensive Treatment Group (%)	Hypoglycemia in Control Group (%)	Morbidity and Mortality
Outpatient Trials					
ACCORD [11]	10,251 outpatients with T2DM with CV disease or CV risk factors	"Hypoglycemia requiring assistance"	3.1 % annually	1 % annually	Stopped after mean of 3.5 years of follow-up due to increase in both all cause (22 %) and cardiovascular (35 %) mortality in the intensive group
ADVANCE [4]	11,140 outpatients with T2DM	<50 mg/dl OR typical symptoms and signs of hypoglycemia without other apparent cause	2.7 % (with at least one severe hypoglycemic episode)	1.5 %	As compared with ACCORD, patients had a shorter duration of diabetes and lower Hba1c values, and fewer were on insulin
VADT [17]	1,791 outpatients with suboptimal response to treatment for T2DM	Not defined	24.1 %	17.6 %	After median follow up of 5.6 years, no significant difference found regarding death, majorcardiovascular events, or microvascular complications, with the exception of progression of albuminuria
Inpatient Trials					
NICE-SUGAR [5••]	6,104 patients expected to require ICU treatment for 3 or more days	≤40 mg/dl	6.8 %	0.5 %	No difference in LOS. Increased mortality in intensive group
VISEP [6]	537 patients with severe sepsis	≤40 mg/dl	17 %	4.1 %	Trend toward prolonged stay in the ICU in intensive group. No difference in mortality.
GLUCONTROL [7]	1,101 patients admitted to 21 ICUs	≤40 mg/dl	8.7 %	2.7 %	Mortality similar in both groups. Trial stopped early due to protocol violations.

T2DM type 2 diabetes mellitus, *CV* cardiovascular, *ICU* intensive care unit, *LOS* length of stay

established coronary artery disease, these effects can induce myocardial ischemia [36].

Several indirect changes also occur that affect inflammatory cytokine secretion, coagulation, fibrinolysis, and endothelial function. Multiple inflammatory markers, including C-reactive protein, IL-6, IL-8, TNF-alpha, and endothelin-1, are increased during episodes of hypoglycemia. This increase in cytokines can lead to endothelial injury, as well as abnormalities in coagulation, both of which can result in an increased risk for cardiovascular events [37, 38]. Some cytokines—namely, IL-1—increase the severity of hypoglycemia, leading to a positive feedback cycle [39]. Increases in epinephrine can cause increased platelet activation, leukocyte mobilization, and blood coagulability [40]. Taken together, these abnormalities could contribute to an increased risk of cardiovascular events with severe hypoglycemia, especially when they occur in patients with preexisting coronary artery disease, a longer duration of diabetes, or severe autonomic neuropathy [18•].

Multiple studies have shown that hypoglycemia can cause changes in baseline EKGs, which places patients at higher risks of arrhythmias, but there is a lack of consensus about the exact changes that occur during hypoglycemia [41–44]. Increased plasma catecholamines and lower levels of serum potassium during hypoglycemia are believed to further augment these arrhythmogenic effects [41]. Hyperinsulinemic hypoglycemia has been linked to changes in atrioventricular conduction, ventricular depolarization, and ventricular repolarization [42]. QT interval prolongation has been the most commonly reported abnormality but is not a consistent finding [44].

Prevention and Treatment of Hypoglycemia During the Hospital Stay

On the basis of the above data, it is clear that prediction and prevention of hypoglycemia should be a priority in order to prevent hypoglycemia and the morbidity and mortality associated with it. There are various strategies involved, and we have divided these into issues to consider at the time of admission, during the hospital stay, and at the time of discharge (Fig. 1).

Considerations on Admission

All patients should be assessed for a history of diabetes, and, if present, the diagnosis, along with the type of diabetes, should be clearly documented in the medical record [20]. All inpatients with known diabetes or with hyperglycemia during their stay should have a hemoglobin A1c level checked, if not performed in the last 2–3 months [20]. For the majority of patients, oral hypoglycemic agents should be discontinued at the time of admission [20]. Patients already on insulin at home should have their dose reassessed on the basis of their clinical status on admission [20]. Prolonged use of 'sliding scale' insulin alone should be avoided [45]. Given the increased incidence of hypoglycemia during the nighttime hours [3], restructuring supplemental insulin dosing protocols to prevent supplemental insulin being given at night is one way to prevent nighttime hypoglycemia [13].

Considerations During the Hospital Stay

Communication

Communication between physicians, nursing staff, and dietary services is essential. Information about nutrition orders, point-of-care orders, and insulin orders all need to be communicated regularly to the appropriate member of the patient's care team. Improvements in care can be accomplished by continued educational training programs of inpatient care teams to update their diabetes knowledge, as well as review adverse events related to diabetes management [20].

Standard Protocols

Structured insulin order sets and management algorithms can improve not only rates of hyperglycemia, but also hypoglycemia [46]. One study showed a 32 % decline in the percent of patient-days with hypoglycemia after the successful implementation of standardized protocols [46]. We recommend having institution-approved standardized order sets for the following scenarios: (1) continuous intravenous insulin infusions, (2) subcutaneous insulin (involving basal insulin, prandial insulin, and corrective insulin), (3) transitioning from intravenous to subcutaneous insulin, and (4) hypoglycemia.

Hypoglycemia management protocols should be linked to protocols for hyperglycemia [16]. The use of nurse-driven hypoglycemia protocols that prompt early treatment of blood glucose values of <70 mg/dl can prevent deterioration of minor events to more serious events [20, 47]. Creation of nursing educational tools that emphasize critical thinking skills when assessing patients receiving insulin can also decrease the incidence of hypoglycemia—for instance, having orders contain contingencies that prioritize patient safety, such as withholding prandial insulin in a patient who is not eating [3].

Quality Improvement

Every hospital should develop a system for tracking the frequency and severity of hypoglycemia and a way to facilitate data analysis and the development of action plans to prevent and/or decrease hypoglycemic events hospital-wide. There are currently no published standardized best methods of addressing hypoglycemia within a hospital system. Measuring glycemic control using glucometrics as developed by the Society of

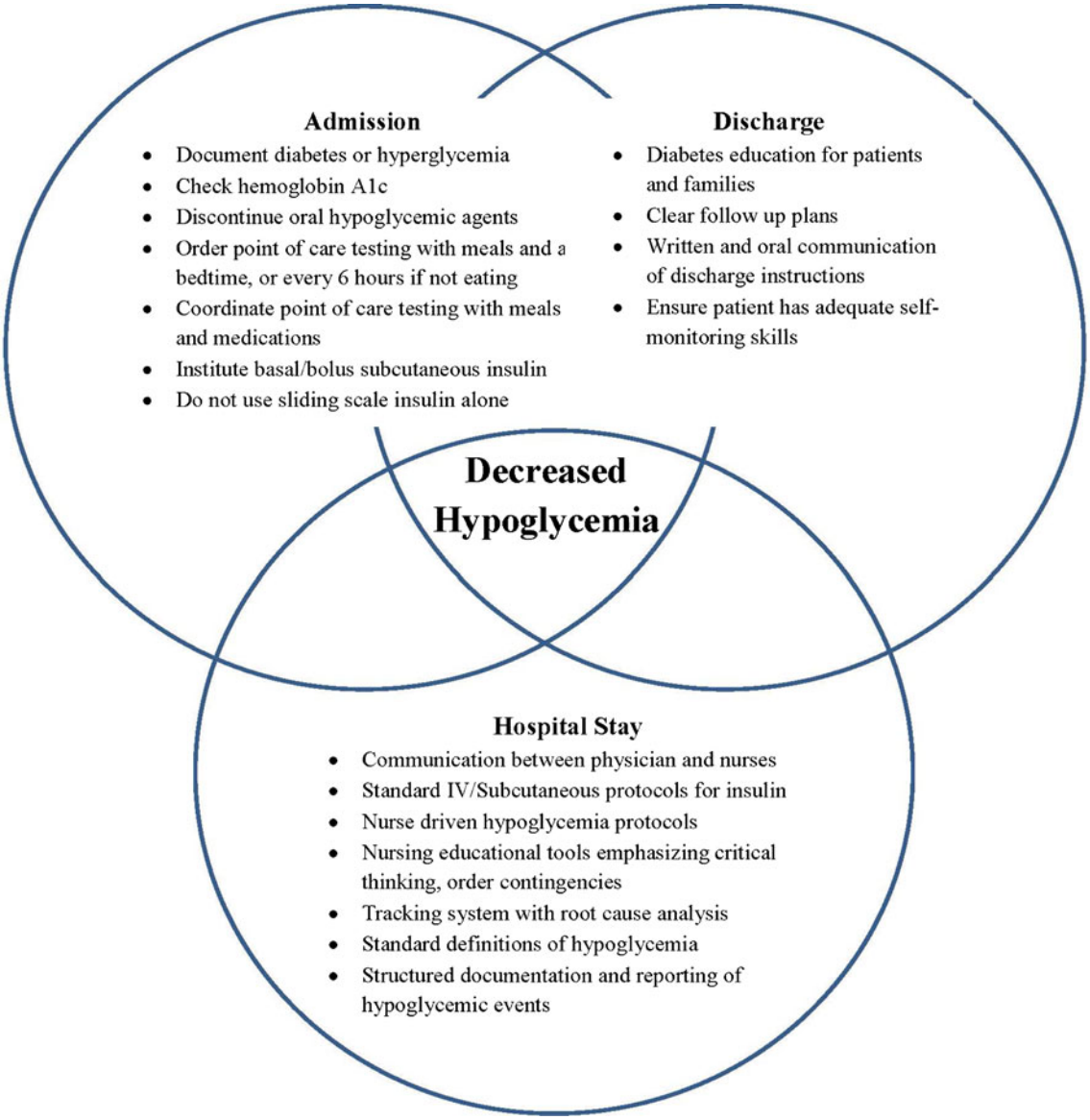

Fig. 1 Prevention and treatment approaches for inpatient hypoglycemia

Hospital Medicine is one possible way of systematically analyzing the impact of hypoglycemia [48]. Performing root-cause analysis for severe hypoglycemia is also advisable.

Monitoring

Hypoglycemia among patients with diabetes should be considered a warning sign of impending clinical deterioration and can be a useful indicator for the need for increased monitoring and more aggressive treatment [2].

The timing of glucose monitoring should match the patient's medication regimen and nutritional intake. In the majority of patients on the general ward who are eating and receiving subcutaneous insulin, blood glucose monitoring should be performed before meals and at bedtime. Patients that are NPO should have their glucose monitored every 4–6 hours [20]. Any glucose value that does not seem to correlate with the patient's clinical status should be confirmed with a plasma glucose sample [13]. Patients receiving intravenous insulin infusions should have their blood glucose monitored every 30 minutes to 2 hours, depending on their most recent blood glucose values [13]. IV insulin should ideally be administered as part of a standardized protocol [13].

Education about risk factors for and ways to avoid hypoglycemia is also necessary to support the protocol, and any hypoglycemic event should prompt a reevaluation of a patient's current insulin regimen in order to help prevent future episodes [16]. In our hospital system, diabetes educators receive a daily hypoglycemia report and, subsequently, contact patients' primary teams to ensure insulin regimens are adjusted accordingly. Implementation of a system to track hypoglycemic events and performance of root-cause analysis can

improve patient safety and decrease risk of future events [20]. Institutions should develop a consistent method of collecting and analyzing glycemic data to in order to monitor the safety and efficacy of the glucose management program [20].

Starting Insulin

In patients with newly diagnosed hyperglycemia or patients on inadequate home regimens, a new insulin regimen needs to be developed. Multiple strategies have been proposed to calculate a total daily dose. In patients who are already receiving intravenous insulin, 80 % of the daily requirement can be used as the total daily dose, and if the patient is eating, 50 % of this should be administered as basal insulin, with the remaining 50 % administered as bolus insulin, divided into three and given prior to meals [49]. If data from an insulin drip are not available, another option is to initiate a total daily dose based on the patient's weight in kilograms. Weight is multiplied by a factor of 0.2–0.5 (depending on patient characteristics and recent blood sugars), and this number is divided into 50 % basal and 50 % bolus, as described above [45]. Supplemental insulin should also be given prior to meals. Insulin doses should be adjusted the following day on the basis of bedside blood glucose measurements and supplemental scale requirements [20, 45]. Insulin doses should be reduced by approximately 20 % if a patient has a blood sugar of <70 md/dl, unless there is a reasonable explanation for this value [20, 45]. Insulin doses should also be reduced if blood glucose levels are between 70 and 100 mg/dl, since these values indicate a potential risk for subsequent hypoglycemia [8•, 20].

Nutrition

A number of factors regarding the content and timing of nutrition can predispose patients to hypoglycemia. There is often a mismatch between meal delivery and prandial insulin administration; additionally, the carbohydrate content of meals can vary significantly. Because of this, we prefer to give mealtime insulin in the form of an insulin-to-carbohydrate ratio, even if this is not the patient's usual outpatient practice. In our institution, trays are brought from the cafeteria with a slip of paper reporting carbohydrate amounts for each food on the patient's tray. The amount of carbohydrate allotted to each person can be determined by the ordering provider. If prandial insulin is given in this manner, the patient receives insulin only for the food actually eaten.

Some situations can be more challenging than others, especially in the case of continuous nutrition, since this is frequently stopped and restarted around times of procedures. In patients receiving enteral or parenteral nutrition, the glucose-monitoring schedule should be individualized but should be frequent enough to detect hyperglycemia during feedings and detect hypoglycemia if feedings are disturbed, usually every 4–6 hours [20]. Our current practice is to use NPH insulin every 8 hours, with glucose monitoring and corrective short-acting insulin every 4 hours, and attach a nursing communication order instructing nurses to page the endocrine consult service as soon as an NPO order is placed. Insulin is either held or decreased at this time, and a dextrose infusion may be initiated if necessary. We use a similar practice when it comes to TPN orders being held or adjusted.

Considerations Around the Time of Discharge

Transitioning from the inpatient to outpatient setting is a time associated with increased medical errors, which can lead to adverse outcomes [50]. When determining a new outpatient diabetes regimen, care should especially be taken when prescribing insulin or oral hypoglycemic agents to the elderly, since a recent hospital discharge is a predictor of serious outpatient hypoglycemia in older patients [51]. Successful transitions require a multidisciplinary team of doctors, nurses, social workers, and diabetes educators [52].

Adequate diabetes education is imperative to ensure that patients and/or their caretakers are comfortable with the discharge regimen and understand how to troubleshoot issues related to hyperglycemia and hypoglycemia after discharge. The discharge plan should be attainable and acceptable to both the patients and their families [52]. Nursing staff should work with patients on self-management skills during their stay to help ensure appropriate administration of their diabetes regimen upon discharge [52]. If applicable, outpatient diabetes education and home health services should be arranged prior to discharge [52].

In patients on new or adjusted diabetes regimens, it is recommended that they be changed to their planned discharge regimen at least 1 day prior to discharge [20]. Standardized written discharge instructions, including medication doses, recommended frequency of monitoring, timing of supplemental insulin, dates of follow-up appointments, and the contact information of providers, can help facilitate a safe transition from the hospital to the outpatient setting [53].

Economic Impact

There is certainly a cost burden associated with managing consequences of inpatient hypoglycemia. Studies have shown trends toward an increased length of stay in both the ICU and the general ward in patients experiencing more frequent hypoglycemia [2, 6]. An increased number of lab draws, point-of-care values, and dextrose infusions also contribute to the overall cost. While there are a number of studies looking at the economic burden of outpatient hypoglycemia, as well as inpatient hyperglycemia, more studies are needed that focus on inpatient hypoglycemia.

Conclusions

Overall, inpatient hypoglycemia is a common problem and has implications for detrimental outcomes for hospitalized patients. It is important to consider patient factors, system factors, and nutrition factors when assessing for risk of inpatient hypoglycemia. Additionally, there are important strategies to consider at the time of admission, in the hospital, and at discharge to optimally prevent and treat hypoglycemia. It is vital that health systems develop closely monitored protocols and policies to avoid hypoglycemia. This will lead to better quality of care and cost saving, which are definitely desired end results.

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Compliance with Ethics Guidelines

Conflict of Interest Leslie Eiland, Whitney Goldner, Andjela Drincic, and Cyrus Desouza declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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