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The Emory University Perioperative Algorithm for the Management of Hyperglycemia and Diabetes in Non-cardiac Surgery Patients

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Abstract Hyperglycemia is a frequent manifestation of critical and surgical illness, resulting from the acute metabolic and hormonal changes associated with the response to injury and stress (Umpierrez and Kitabchi, Curr Opin Endocrinol. 11:75–81, 2004; McCowen et al., Crit Care Clin. 17(1):107–24, 2001). The exact prevalence of hospital hyperglycemia is not known, but observational studies have reported a prevalence of hyperglycemia ranging from 32 to 60 % in community hospitals (Umpierrez et al., J Clin Endocrinol Metab. 87(3):978–82, 2002; Cook et al., J Hosp Med. 4(9):E7–14, 2009; Farrokhi et al., Best Pract Res Clin Endocrinol Metab. 25(5):813–24, 2011), and 80 % of patients after cardiac surgery (Schmeltz et al., Diabetes Care 30(4):823–8, 2007; van den Berghe et al., N Engl J Med. 345(19):1359–67, 2001). Retrospective and randomized controlled trials in surgical populations have reported that hyperglycemia and diabetes are associated with increased length of stay, hospital complications, resource utilization, and mortality (Frisch et al., Diabetes Care 33(8):1783–8, 2010; Kwon et al., Ann Surg. 257(1):8–14, 2013; Bower et al., Surgery 147(5):670–5, 2010; Noordzij et al., Eur J Endocrinol. 156(1):137–42, 2007; Mraovic et al., J Arthroplasty 25(1):64–70, 2010). Substantial evidence indicates that correction of hyperglycemia reduces complications in critically ill, as well as in general surgery patients (Umpierrez et al., J Clin Endocrinol Metab. 87(3):978–82, 2002; Clement et al., Diabetes Care 27(2):553–97, 2004; Pomposelli et al., JPEN J Parented Enteral Nutr. 22(2):77–81, 1998). This manuscript reviews the pathophysiology of stress hyperglycemia during anesthesia and the perioperative period. We provide a practical outline for the diagnosis and management of preoperative, intraoperative, and postoperative care of patients with diabetes and hyperglycemia.

Keywords Perioperative · Diabetes and surgery · Stress hyperglycemia · Surgery · Anesthesia · Inpatient care · Hospital · Blood glucose management

This article is part of the Topical Collection on *Hospital Management of Diabetes*

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Introduction: Hyperglycemia and Perioperative Outcomes

Extensive observational and prospective randomized trials have shown that hospitalized patients with hyperglycemia have poor clinical outcomes compared to cohorts who maintain a euglycemic state [1, 2, 3•, 4, 5, 6••, 7]. The majority of the evidence demonstrating that hyperglycemia worsens outcomes stems from cardiac surgery and critically ill patients admitted to surgical intensive care units [8–10]. In this setting, observational and prospective clinical trials have shown that hyperglycemia is associated with increased rates of hospital

complications and mortality [4, 11–14] and that improved glycemic control reduces multi-organ failure, systemic infections, and short- and long-term mortality [8, 15]. A retrospective analysis of 61,000 patients undergoing elective non-cardiac surgery demonstrated that 1-year mortality was significantly related to preoperative blood glucose (BG); crude incidence of mortality at 1 year for a preoperative BG 60–100 mg/dL was 3–5 versus 12 % in patients with BG >216 mg/dL [16].

Hyperglycemia is also associated with increased risk of perioperative complications in general non-cardiac surgery [2, 6••, 17, 18]. Patients with glucose levels between 5.6 and 11.1 mmol/L (110–200 mg/dL) versus patients with glucose levels >11.1 mmol/L (>200 mg/dL) had respectively, a 1.7-fold and 2.1-fold increased mortality compared to those with glucose levels <5.6 mmol/L (<110 mg/dL) [19]. The risk of postoperative wound infection in patients undergoing general surgery increases approximately 30 % for each 40 mg/dL increase in BG [20]. General surgery patients with glucose levels of >12.2 mmol/L (>220 mg/dL) on the first postoperative day have a 2.7-fold increased rate of infection [19]. In addition, hyperglycemia is a risk factor for the development of postoperative pneumonia and acute kidney injury [2].

Several cross-sectional studies have shown that the risk of complications and mortality relates to the severity of hyperglycemia, with a higher risk observed in patients without a history of diabetes (new onset and stress-induced hyperglycemia) compared to those with a known diagnosis of diabetes [1, 2, 5, 6••]. A study of general hospital admissions reported that patients with newly recognized hyperglycemia had a longer length of hospital stay and higher admission rate to an intensive care unit. They were also less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility [1]. Kwon et al. [3•] found that nondiabetic patients with perioperative hyperglycemia had nearly twice the risk of infection, re-operative intervention, and in-hospital death as diabetic hyperglycemic patients. Frisch et al. [2] found an increased risk of 30-day mortality in nondiabetic patients with hyperglycemia when compared to patients with diabetes. More recently, Kotagal et al. [6••] reported a dose-response relationship between glucose levels and a composite of adverse events [odds ratio (OR), 1.3 for BG 125–180 (95 % confidence interval (CI), 1.1–1.5); OR, 1.6 for BG ≥180 (95 % CI, 1.3–2.1)]. Conversely, diabetic patients with hyperglycemia, including those with BG ≥180 mg/dL, did not have an increased risk of adverse events (OR 0.8; 95 % CI 0.6–1.0).

Mechanisms Underlying the Detrimental Effects of Hyperglycemia

Acute illness, anesthesia, and surgery result in metabolic perturbations that alter glucose homeostasis [20–22] and hyperglycemia is common in hospitalized patients [23]. Stress conditions raise levels of counter-regulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone. This response results in a number of alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency [22, 24]. Epinephrine stimulates glucagon secretion and inhibits insulin release by pancreatic β cells [25]. High cortisol levels increase hepatic glucose production and stimulate protein catabolism and increased gluconeogenesis [26, 27].

The development of hyperglycemia leads to generation of reactive oxygen species and elevated inflammatory markers [28–30]. The release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1β contributes to an insulin resistant state [28]. Increasing evidence suggests that TNF-α interferes with insulin receptor signaling [31–33] as well as the synthesis and/or translocation of the glucose transporter GLUT-4 to the plasma membrane [34]. This has been suggested to contribute to insulin resistance in peripheral tissues resulting in diminished insulin action. The natural stress response contributes to both hyperglycemia and insulin resistance, making the maintenance of glycemic control more difficult in the perioperative period. This places the surgical population at risk for complications related to hyperglycemia in both diabetics and nondiabetics.

The exact mechanism relating hyperglycemia to poor outcomes has yet to be elucidated. Poor wound healing and an increased infection risk have been demonstrated in surgical patients with diabetes. Hyperglycemia has been shown to impair leukocyte function and to limit phagocytosis, chemotaxis, and bacterial destruction [35–37]. Hyperglycemia limits neovascularization and collagen synthesis, restricting the body's ability to generate new and healthy tissue at the surgical site. The presence of inflammatory cytokines and state of relative insulin-resistance promote lipolysis, increasing the release of free fatty acids (FFAs). Elevated FFAs have detrimental effects on the cardiovascular system by increasing catecholamine concentrations and mean arterial blood pressure [38]; they are associated with malignant cardiac dysrhythmias [39, 40], increased myocardial oxygen consumption [40], and presence of ischemic stroke [41].

Hyperglycemia also results in increased platelet aggregation and a pro-thrombotic state [42]. An overproduction of reactive oxygen species can result in direct cellular damage, vascular, and immune dysfunction [43, 44]. NF-kB activation and the production of inflammatory cytokines like TNF-α, IL-6, and plasminogen activator inhibitior-1 (PAF-1) increase vascular permeability and activate both leukocytes and platelets [25, 45, 46]. Hyperglycemia-induced oxidative stress adversely affects hemostasis; circulating soluble tissue factor and thrombin-antithrombin

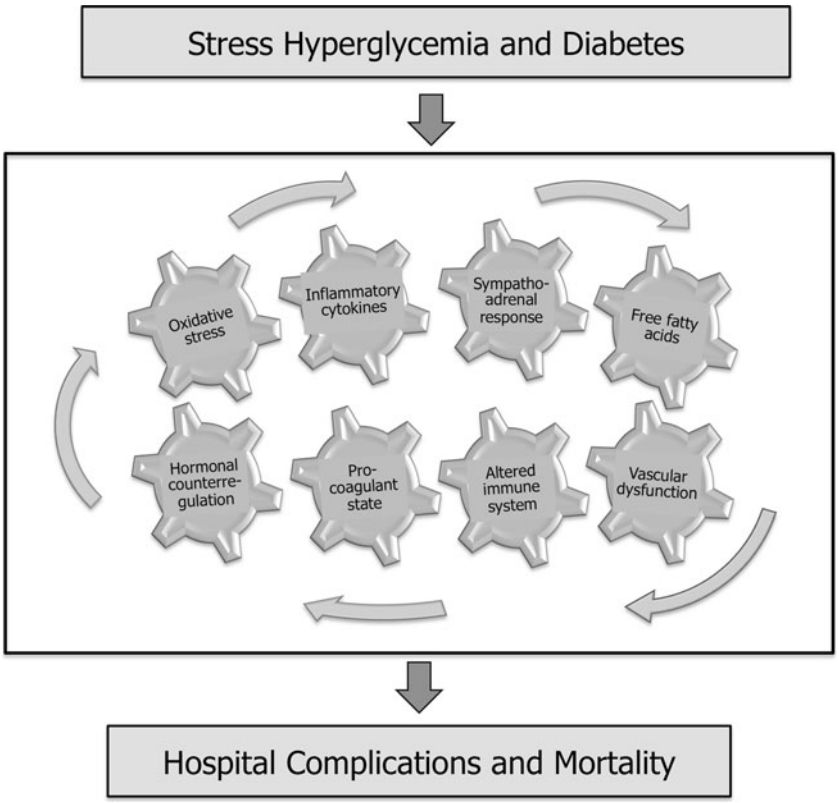

Fig. 1 Mechanisms underlying the detrimental effects of stress hyperglycemia and diabetes during hospitalization

complex levels are increased [46] and platelet aggregation is potentiated [47] (Fig. 1).

Target Blood Glucose Levels

The literature supports prevention of both hypoglycemia and hyperglycemia; however, the ideal range between these two points remains to be determined. The AACE/ADA consensus statement supports less aggressive therapy for critically ill patients (target 140–180 mg/dL) than previously recommended [48, 49]. The Society of Critical Care Medicine recommendations vary based on patient population, but trigger for treatment in all non-cardiac patients is 150 mg/dL [50]. Non-critical care goals are similar and generally, glucose values less than180 mg/dL are acceptable for general surgical patients based on their oral intake status [51, 52].

Emory University Perioperative Glycemic Algorithm

Given the increasing number of patients with diabetes and the high risk of perioperative complications in patients with hyperglycemia, a multidisciplinary task force of physicians developed a glucose management algorithm for non-cardiac elective surgery at Emory University. We specifically addressed the following areas:

- Preoperative screening and assessment of diabetic patients
- A perioperative glycemic monitoring and treatment plan
- Postoperative order sets for patients with type 1 and type 2 diabetes, and for stress hyperglycemia
- Post-discharge planning including medication initiation and adjustments
- A hypoglycemia management protocol.

Preoperative Glycemic Evaluation

Diabetes and hyperglycemia risk is evaluated prior to elective surgery in the Anesthesia Preoperative Clinic (APC) visit. Nondiabetic patients aged 45 years or older, or with a BMI ≥25 kg/m^2, undergo glycated hemoglobin (HbA_1c) testing if not performed within the last 3 months to rule out undiagnosed diabetes and to ensure appropriate treatment and follow-up care during the perioperative period [53]. Patients with diabetes are noted as type 1 or 2, and for patients managed with insulin, the total daily dose (TDD) is recorded. All patients with type 2 diabetes are classified according to their insulin sensitivity. For patients who later develop hyperglycemia during hospitalization but who do not have a history of diabetes, HbA_1c ≥6.5 % suggests that diabetes preceded hospitalization. If HbA_1c is not drawn in APC because patients do not meet

initial criteria, this test may be sent during the hospitalization following demonstrated hyperglycemia.

Data are mixed supporting the association between elevated HbA_1c and surgical complications. Although several investigators have reported higher risk for postoperative complications and mortality in patients with high HbA_1c, a large retrospective study of 55,000 patients failed to demonstrate an increased incidence of complications and wound infections [54–58]. Recently, reducing $HgbA_1C$ to less than 8 % improved glycemic control on the day of surgery [59]. However, no optimal HbA_{1C} concentration has been determined, nor is there evidence that delaying surgery to achieve this goal improves outcomes. At this time, our hospital does not routinely delay surgery for poorly controlled diabetes.

Preoperative Glycemic Management

Prior to developing an institutional plan, it was recognized that varied providers offered vastly different preoperative instructions to patients regarding diabetes medications on the day before and day of surgery. Fear of hypoglycemia frequently led to the inappropriate practice of withholding all drug therapy in patients with diabetes. To ensure safety, the protocol includes recommendations for antecedent medication to ensure all patients receive best-fit instructions for their type of diabetes. Table 1 summarizes preoperative medication management.

Treatment recommendations for type 2 diabetes using home medications are generally categorized based on the type of diabetes, nature and extent of the surgical procedure, antecedent pharmacological therapy, and state of metabolic control prior to surgery [10, 60]. Patients with type 2 diabetes controlled with diet and exercise do not need medication therapy prior to coming to the hospital for surgery. In general, all patients with type 1 diabetes undergoing minor or major surgical procedures require insulin during the perioperative period. In such patients, the stress of surgery may result in the development of diabetic ketoacidosis or hyperosmolar hyperglycemic state, with negative prognostic consequences [61–63].

Oral Anti-Diabetic Agents

It has been recommended that oral agents be discontinued the day before surgery as means to limit the risk of hypoglycemia or other metabolic derangements associated with these drugs [52, 64]. In contrast, the Joint British Diabetes Societies guidelines [51] for the perioperative management of the adult patient recommends that, for patients undergoing a short starvation period (one missed meal only), metformin can be continued unless the patient is on a three-times-per-day regimen, when the middle dose should be omitted. In renal impairment, metformin should be stopped when the preoperative fast begins and restarted postoperatively once the patient is eating again. SAMBA states that metformin may be taken the day before

Table 1 Preoperative diabetes medication adjustment in general surgery

Medication use on the day prior to surgery

Oral Agents		Glargine or Detemir		NPH or 70/30 insulin		Lispro, aspart, glulisine, regular		Non-Insulin Injectables	
AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose
Usual dose	Usual dose	Usual dose	80 % of usual dose	Usual dose	80 % of usual dose	Usual dose	Usual dose	Usual dose	Usual dose

Medication use on the day of surgery

Oral Agents	Glargine or Detemir	NPH or 70/30 insulin	Lispro, aspart, glulisine, regular	Non-Insulin Injectables
Hold	80 % of usual dose	50 % of usual dose if BG > 120mg/dL	Hold if NPO	Hold

surgery, but should not be taken on the day of surgery until normal diet is resumed [64]. Given the mixed information available, our algorithm, based on the limited literature and the drug's expected pharmacokinetics/dynamics, recommends holding the use of oral agents, including metformin, on the day of surgery. The efficacy and safety of metformin in the hospital has not been prospectively established. Although the risk is low, inpatient use of metformin may be associated with a the development of lactic acidosis in patients with disorders associated with increased generation of lactate acid or in impaired clearance of metformin such as impaired renal function (eGFR <30 mL/min per 1.73 m2), liver failure, severe hypoxia, heart failure, surgery, and alcohol use. Sulfonylureas and other insulin secretogogues should be avoided in the hospital because of the increased risk of hypoglycemia [48, 52, 65, 66].

The safety and efficacy of DPP-4 inhibitors for the management of inpatient hyperglycemia were evaluated in a randomized pilot study in patients with type 2 diabetes treated at home with diet, oral antidiabetic agents, or a low daily insulin dose (≤0.4 units/kg/day) [67•]. In this trial, patients were randomized to sitagliptin alone, sitagliptin combined with low-dose glargine insulin, or to a basal bolus insulin regimen, plus supplemental doses of insulin lispro. All treatment regimens resulted in similar improvement in mean daily BG concentration. However, patients with an admission glucose >180 mg/dL in the sitagliptin group had higher mean daily BG compared with patients treated with basal-bolus or sitagliptin plus glargine. Several large multi-center randomized clinical trials are currently investigating the safety and efficacy of DPP-4 inhibitors therapy in general medicine and surgical inpatients with type 2 diabetes.

Insulin Therapy

Several guidelines including those issued by the ADA [49], Endocrine Society [52], SAMBA [64], and the Joint British Diabetes Societies [51] have recommended continuation of basal insulin (glargine or detemir) on the evening prior to surgery. It has been suggested that the patients usual dose be reduced to between 75 and 80% of their normal basal insulin, according to eh patient's usual glucose control [68, 69]. Patients treated with NPH insulin or with premixed formulations should take 80 % of the evening dose the day before surgery, and half of the morning dose the day of surgery. To prevent hypoglycemia, patients with type 2 diabetes with fasting glucose less than 120 mg/dL on the day of surgery should hold the morning dose of NPH or premixed insulin. As an alternative, patients using NPH can receive half of the daily dose if concurrently administered a dextrose solution to maintain BG within target range. Consideration for preoperative insulin should include frequency of dosing, type of insulin, morning BG, and scheduled time of surgery.

Day of Surgery Hyperglycemia

Currently, there are no guidelines for the threshold at which surgery should be cancelled in the setting of hyperglycemia. SAMBA recommends that in the setting of "severe dehydration, ketoacidosis (DKA), and hyperosmolar nonketotic states" surgery should be postponed [64]. Elective surgery is delayed for minimally 12 h if there is evidence of ketosis (by urine ketones or blood chemistry) or signs of hyperosmolar hyperglycemic non-ketotic state (weakness, lethargy, confusion) in the setting of supportive lab values. In the absence of these findings, an insulin drip or subcutaneous insulin can be administered to achieve BG levels <300 mg/dL. If BG levels drop as expected within 1 h, insulin treatment is continued and the patient may proceed to the operating room for surgery. If persistent hyperglycemia occurs (BG ≥300 mg/dL), surgery is postponed for continued treatment.

Glucose Monitoring During the Perioperative Period

Capillary point of care (POC) testing is completed using a monitoring device with demonstrated accuracy in the hospital setting. Patients with a BMI ≥25 kg/m^2 or age ≥45 years are tested on arrival for elective surgery. If the fasting BG >140 mg/dL, continued monitoring and treatment is initiated in the operating room and postoperative anesthesia care unit (PACU). Patients with a fasting BG ≤140 mg/dL are not monitored in the operating room (OR); however, POC testing is repeated the PACU to re-check for stress hyperglycemia following surgery. Blood glucose is also measured in all patients with history of diabetes at arrival to the pre-surgery holding area. Blood glucose monitoring is indicated before and every 2 h during surgery and immediately after surgery in patients with a history of diabetes (Fig. 2).

When patients are transferred to a hospital floor bed, BG monitoring is indicated before meals and at bedtime. Both those with demonstrated surgical or postoperative hyperglycemia, and those with a known history of diabetes, need to continue routine inpatient testing. Pre-meal POC testing should be obtained close to the time of the meal tray delivery and no longer than 1 h before meals. For patients who are NPO or receiving continuous enteral nutrition, POC testing is recommended every 4–6 h.

Management of Hyperglycemia in Critically Ill Surgical Patients (OR and ICU)

Intravenous insulin is the preferred medication to maintain normoglycemia in critically ill patients in the operating room and ICU. The short half-life of IV insulin (35 min) allows easy titration and discontinuation in the event of unpredicted

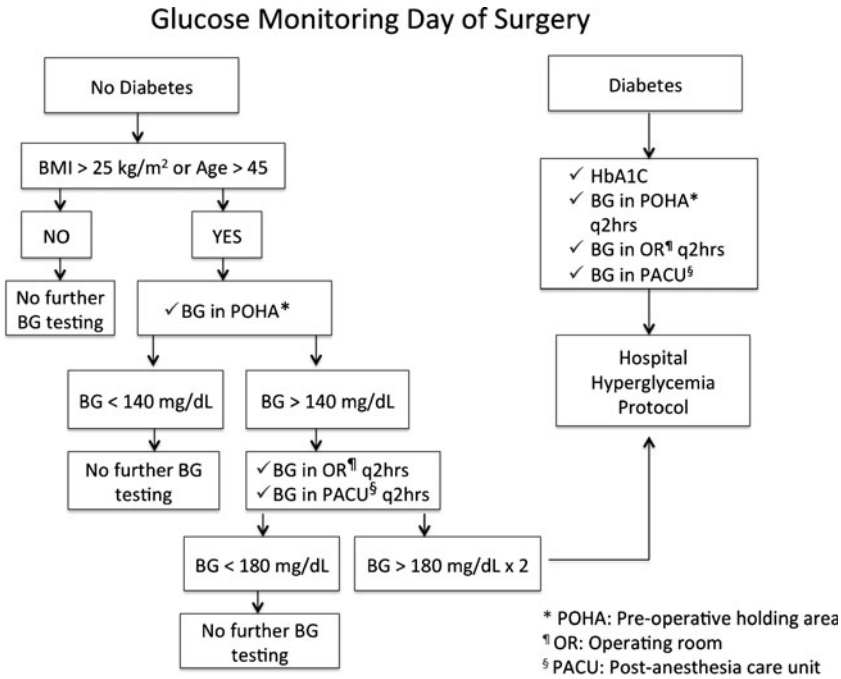

Fig. 2 Perioperative glucose monitoring in inpatients

changes in patient's health, concurrent medications, and nutrition. An insulin infusion should be started in the operating room or ICU when a patient's BG is ≥180 mg/dL. A variety of insulin protocols have been shown to be effective in achieving glycemic control, while minimizing hypoglycemic events and improving hospital outcomes [9, 15, 70–74].

A proper protocol allows for a flexible BG target that is modified to best care for a patient given their clinical condition. We based our variable insulin infusion protocol upon resources within the Emory Healthcare System; we suggest that each hospital address their patient population, staff/personnel, and equipment when designing a continuous insulin infusion algorithm. Essential elements that increase protocol success and safety need to base rate adjustments on the following: (1) the current and previous glucose value, (2) the recent rate of insulin infusion, (3) the change (or lack of change) from the previous reading, (4) the frequency that normoglycemia has been achieved on BG checks, and caloric intake by administration of oral feedings or by enteral/parenteral nutrition support [25, 75, 76].

Several computer-based algorithms are commercially available to direct nursing staff adjustments of the infusion rate [72, 77, 78]. Glycemic control using computer-guided algorithms has been demonstrated in controlled trials. As compared to standard paper protocols in ICU, computer-based algorithm demonstrates more rapid achievement of target BG levels, as well as decreased variability in BG range. Despite differences in glycemic control, it appears that there are no major differences between computerized protocols versus conventional glucose control [72, 79, 80]. Thus, most insulin algorithms are appropriate for the management of hyperglycemia in critically ill patients, and the choice depends on physician's preferences and cost considerations [15, 50, 71, 81].

The transition from IV to SC insulin as patients move from an ICU to surgical floor environment is based on recommendations from the 2009 ADA Consensus Statement on Inpatient Hyperglycemia [49]. Eighty percent of the 24 hour insulin dose is calculated as the TDD subcutaneous dose; 70 % of this is administered as basal insulin and 30 % as prandial (when the patient is eating a normal diet). At Emory, a critical care pharmacist supervises the order transition to ensure accuracy and safety of the floor order set. Subcutaneous insulin glargine is administered 2–4 h before discontinuation of the insulin infusion. Most patients without a history of diabetes (HbA_{1C} <6.5 mg/dL) and an insulin infusion rate ≤2 U/h can be controlled with correctional insulin only and do not need transition to basal or basal bolus insulin regimen [79].

Management of Intra-Operative Hyperglycemia in Non-critically Ill Patients

There has been a shift to prefer the use of subcutaneous (SC) rapid acting insulin analogs over regular insulin for correction of hyperglycemia in ambulatory surgery and for patients undergoing "short-procedures" [51, 64, 82, 83]. Many reviews suggest that time be a determining factor for the type of insulin used in the operating room; shorter procedures are often less associated with fluid shifts, temperature changes, and

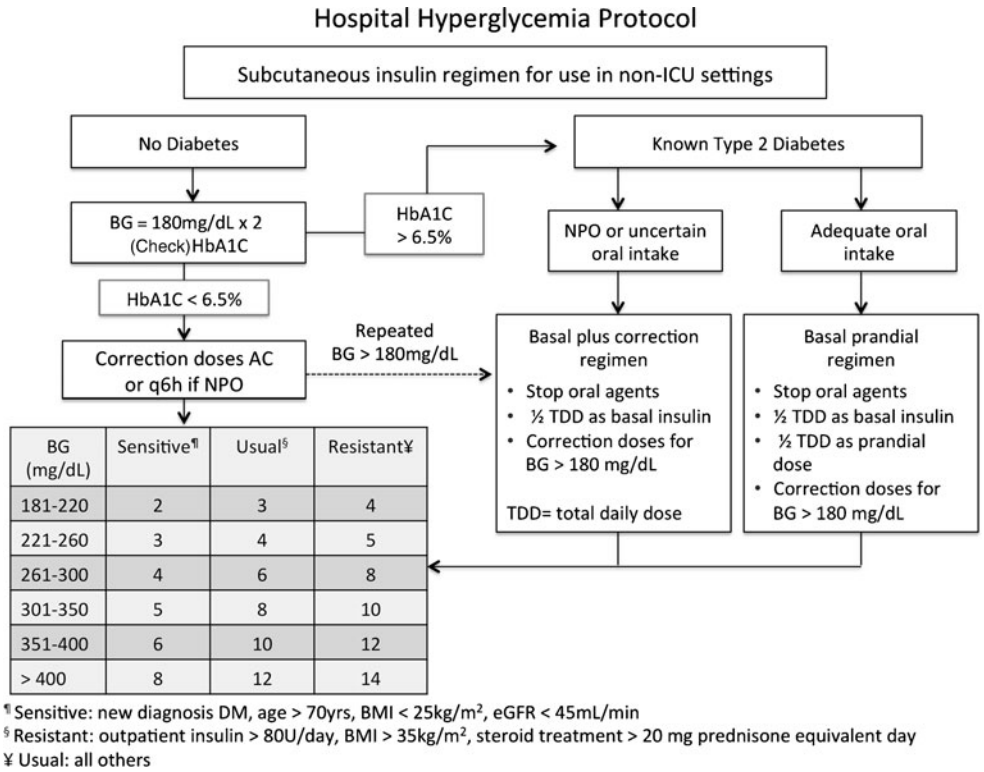

Fig. 3 Hospital hyperglycemia protocol

metabolic derangements. Furthermore, short procedures may only require a single dose of subcutaneous insulin. The onset time of insulin analogs is between 15–30 min and they peak in 1–1.5 h; this limits the risk of "insulin stacking" which has been associated with repeated doses of SC regular insulin [84]. Likewise, the Endocrine Society and SAMBA recommend the use of SC over IV insulin for correction of hyperglycemia in non-critically ill general surgery patients [52, 64]. Advantages of SC rapid-acting insulin analogs include ease of administration, low rate of hypoglycemia, and efficacy in correcting hyperglycemia [84–87].

Our SC dosing algorithm is based upon the patient's expected response to insulin. As mentioned previously, a patient is stratified into one of three groups preoperatively (insulin sensitive, regular or resistant) and this classification is used for both intraoperative and postoperative insulin dosing. Blood glucose is checked every 2 h from arrival in the preoperative area through PACU. If indicated, subcutaneous insulin is administered following testing to prevent hyperglycemia. Treatment should be initiated at any point during the surgical period for patients with BG levels ≥180 mg/dL (Fig. 3).

Management of Postoperative Hyperglycemia

Glucose control in general surgery non-ICU patients should be managed with subcutaneous insulin (Fig. 3). Several studies have demonstrated that management of hyperglycemia with sliding scale insulin (SSI) insulin alone results in poorly controlled BG levels, resulting in both hypoglycemia and hyperglycemia [88–90].

Table 2 Starting subcutaneous basal and prandial insulin for patients with a new diagnosis of type 2 diabetes or those treated with diet or oral agents at home

	Insulin sensitive	Usual insulin needs	Insulin resistant
Total insulin daily dose	0.2 U/kg/day	0.4 U/kg/day	0.5 U/kg/day
Uncertain oral intake or NPO			
Basal (glargine or detemir)	0.1 U/kg/day	0.2 U/kg/day	0.25 U/kg/day
Regular diet			
Basal (glargine or detemir)	0.1 U/kg/day	0.2 U/kg/day	0.25 U/kg/day
Prandial (lispro, aspart, or glulisine)	0.1 U/kg/day	0.2 U/kg/day	0.25 U/kg/day

Scheduled subcutaneous basal insulin with glargine or detemir given once daily, in combination with short (regular) or rapid acting insulin (lispro, aspart, glulisine) prior to meals, is effective and safe for the management of hospitalized patients with diabetes [72, 88, 91, 92•, 93]. The Basal Plus approach [89, 93] includes a single daily dose of basal insulin (glargine or detemir) and has been shown to be as effective as the basal bolus regimen in most general surgery patients with type 2 diabetes. As a patient is able to tolerate a normal diet, nutritional insulin is added to the regimen and the basal bolus approach is used. Correctional insulin is provided to patients with BG >180 mg/dL during their hospital course (Table 2). For those already on home insulin, basal therapy is calculated using the 50 % of their TDD. The remainder is ordered as prandial short-acting insulin when the patient has reasonable oral intake. Correctional insulin is provided to all diabetic patients as needed to keep pre-meal BG ≤140 mg/dL. Adjustments to basal dosing are suggested in the algorithm for patients with mean daily BG >180 mg/dL. Endocrine consultation is recommended for continued hyperglycemia despite dosing changes. Additional triggers for expert involvement include repeated hypoglycemia, diabetic patients on dialysis, transplant patients, those on high dose steroids, TPN initiation, and patients with type 1 diabetes using a subcutaneous insulin pump.

Correctional insulin is provided to patients who experience stress hyperglycemia (BG >180 mg/dL) during their hospital course. These patients are monitored every 6 h and treated with short-acting insulin as needed. Point-of-care testing is discontinued in these patients when BG values are <140 mg/dL without insulin therapy for 24 h [45, 52].

Management of Hospitalized Patients with Type 1 Diabetes

Patients with type 1 diabetes have minimal to absent pancreatic beta cell function and rely on the exogenous administration of insulin to maintain glucose homeostasis. They have worse glycemic control and higher rates of acute kidney injury compared to patients with type 2 diabetes; however, the impact of inpatient glycemic control on clinical outcomes has not been determined in patients with type 1 diabetes [61]. Insulin therapy must provide both basal and nutritional components to achieve the target goals. It is important to inquire directly from the patient times and doses of prescribed insulin, medication adherence, recent dietary habits, including changes in appetite, and level of physical activity, to guide insulin therapy.

On the day of surgery, an intravenous insulin infusion is used in the operating room and POC testing completed every hour for procedures lasting >2 h. If the procedure is expected to be short, patients have hourly POC testing and treatment with SC rapid-acting analogs for BG ≥180 mg/dL. Postoperatively, 80 % of the patient's TDD is administered as basal insulin. When eating, the patient's home dose of prandial insulin is initiated. Blood glucose is checked four times daily and correctional insulin is provided for BG ≥180 mg/dL.

Roughly 400,000 patients in the USA who have type 1 diabetes use insulin pumps. Successful management of inpatient diabetes with the continuation of insulin pump therapy has been previously demonstrated in selected patients [75, 94, 95]. However, current recommendations advocate for the establishment of clear policies and procedures to guide patients and hospital staff in the management of diabetes with the use of insulin pumps [96]. Clear physician's orders with specifics on the type of diet, frequency of POC glucose testing, basal rate, bolus, and correctional insulin settings should also be in place. A patient-staff pump/glucose log that records time and date of POC glucose value, basal insulin rate, bolus and correctional insulin used, carbohydrates consumed, and infusion site changes should be continuously updated and kept by the patient's bedside. The patient's cognitive, emotional, and physical ability to manage his/her insulin pump during the hospitalization should also be considered when deciding to continue using the pump while the patient is hospitalized.

Prompt involvement of inpatient diabetes specialists are recommended in our hospital algorithm to assist with the assessment and management of patients with type 1 diabetes using insulin pumps [52, 84, 97]. If inpatient diabetes resources are not available, discontinuation of insulin pump and transition to multi-dose injections (a pump holiday) may be the safest and most appropriate step. The total daily insulin dose can be calculated by adding basal rate(s) plus average prandial insulin requirements on pump settings to give a similar basal (glargine or detemir) and prandial (lispro, aspart or glulisine) insulin doses in a basal bolus regimen.

Hypoglycemia

Hypoglycemia is the most common treatment side effect of insulin in the hospital setting. It presents a major barrier to satisfactory long-term glycemic control. For the purpose of hospital inpatients, hypoglycemia is defined as any glucose level <70 mg/dL (3.9 mmol/L) [49, 52, 84, 98]. Severe hypoglycemia has been defined as <40 mg/dL (2.2 mmol/L). Hypoglycemia is associated with both immediate and delayed adverse clinical outcomes [99–101]. Hypoglycemia is an independent risk factor for morbidity and mortality in hospitalized patients [102] and is associated with prolonged QT

interval, ischemic electrocardiogram changes, angina, arrhythmias, and sudden death [103–105].

Hypoglycemia may go unrecognized under anesthesia [106, 107]; thus, frequent monitoring is indicated for patients in the perioperative period. A root cause analysis of >80,000 patients demonstrated that intraoperative hypoglycemia is rare; only 17 patients had a documented value of BG ≤40 mg/dL. Commonly cited factors contributing to intraoperative hypoglycemia were lack of communication between teams, failure to monitor BG levels during surgery, and inadequate treatment of preoperative hypoglycemia [107]. If a patient's BG is less than 80 mg/dL in the preoperative area or in the operating room, a dextrose-containing intravenous solution (dextrose 5 % or 10 %) started at 100–150 ml/h or 50–75 ml/h, respectively, is indicated. Blood glucose monitoring is increased to every 15 min until levels are sustained at 100 mg/dL on two consecutive measurements. After surgery, if the patient is alert and able to eat/drink, hypoglycemia can be treated with 15–30 g carbohydrate administration (orange juice, crackers). Postoperatively, it is important to design an order algorithm that can be deployed by nurses to provide immediate treatment for those patients with BG ≤70 mg/dL.

Transition from Hospital to Home

Few studies have focused on the optimal management of hyperglycemia and diabetes after hospital discharge. Although insulin is used for most patients with diabetes in the hospital, many patients do not require insulin after discharge. The Endocrine Society's 'Inpatient Guidelines for the Management of Non-ICU Patients with Diabetes,' and a recent study from our group, recommended the use of HbA_{1C} to tailor treatment regimen at discharge. Use of this medication adjustment algorithm at discharge significantly improved glycemic control by ~1.5 % HbA_{1C} reduction after 12-week follow-up [89]. Patients with acceptable diabetes control (HbA_{1C} <7–8 %) can be discharged on their pre-hospitalization treatment regimen (noninsulin agents and/or insulin therapy) if there were no contraindications to therapy. Patients with suboptimal control should have intensification of therapy usually by either the addition of or increase in noninsulin agents or basal insulin. Those with HbA_{1C} between 8 and 10 % are discharged on non-insulin agents plus basal insulin at 50 % of the hospital dose. Any patient with HbA_{1C} >10 % should be considered a candidate for a basal bolus insulin regimen.

The transition of care from the inpatient to the outpatient setting is an important national priority. The 2013 National Patient Safety Goals include goals and requirements for hospital discharge planning and transitional care [108]. Unfortunately, transition from hospital to home does not always go smoothly resulting in an adverse event, poor glycemic control, increased rate of emergency room visits, and higher hospital readmission rates and costs [109–111]. At our institution, a nursing team provides patient education regarding self-monitoring, diet therapy, medication instructions, and management of hyper/hypoglycemia. Social workers are available to assist with financial resources to obtain medication and supplies should the patient not have medical insurance or financial means to purchase needed therapies. Arrangements for follow-up are made through The Emory Clinic physicians or the patient's current primary care provider.

Conclusion

In this article, we present a universal insulin algorithm for the perioperative management of hyperglycemia and diabetes implemented at Emory University Hospital.

Inpatient hyperglycemia is common and associated with increased risks of complications in patients with or without diabetes. Correction of hyperglycemia with insulin administration has been shown to improve clinical outcomes. Existing clinical evidence favors insulin over other antidiabetic agents in achieving and maintaining glycemic control in hospitalized patients. In the critically ill, IV insulin infusion is most appropriate, with a starting treatment threshold no higher than 180 mg/dL. Target range for patients on an insulin infusion is 140–180 mg/dL.

In non-critically ill patients, rapid-acting subcutaneous insulin can be used to achieve glycemic control in the operating room for both diabetic patients and those with stress hyperglycemia. Transition to basal-bolus regimen is appropriate for the surgical floor and has been shown to improve glycemic control and reduce perioperative complications in surgical patients [89, 92•, 93]. In patients with poor or uncertain oral intake, as is common in the surgical population, a single-dose of basal insulin is preferred. Recent preliminary data suggest that incretin therapy (DPP-4 inhibitors) may represent an alternative to insulin in patients with mild to moderate hyperglycemia in the perioperative period [67•].

Multiple teams care for a surgical patient during the hospital course (anesthesiology, surgery, critical care medicine, internal/hospital medicine, and endocrinology). Our algorithm provides recommendations for the initial patient preoperative visit through hospital discharge. Creating standard screening, monitoring, and treatment allows our institution to better care for patients and also serves to ease transitions of care amongst teams. This includes attention to discharge needs as

means to prevent emergency room visits, readmissions, and future hospitalizations. There is vast opportunity to improve clinical outcomes related to glycemic control in this population.

Compliance with Ethical Standards

Conflict of Interest Drs. Duggan, Klopman, and Berry declare no conflict of interest. Dr. Umpierrez is supported in part by research grants from the American Diabetes Association (1-14-LLY-36), PHS grant UL1 RR025008 from the Clinical Translational Science Award Program (M01 RR-00039), and grants from the National Institute of Health and the National Center for Research Resources. He has received unrestricted research support for inpatient studies (at Emory University) from Merck, Novo Nordisk, Astra Zeneca, Boehringer Ingelheim, and Sanofi, and has received consulting fees or/and honoraria for membership in advisory boards from Novo Nordisk, Sanofi, Merck, and Boehringer Ingelheim and Regeneron.

Human and Animal Rights and Informed Consent This article is an algorithm based upon previously published studies including those done by Dr. Umpierrez. Refer to original articles for information regarding informed consent of study subjects.

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- • Of importance
- •• Of major importance

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