

# Management of diabetes mellitus in hospitalized patients

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Literature review current through: Jan 2024.

This topic last updated: Jan 04, 2024.

### **INTRODUCTION**

Patients with type 1 or type 2 diabetes mellitus are frequently admitted to a hospital, usually for treatment of conditions other than the diabetes [1,2]. In one study, 25 percent of patients with type 1 diabetes and 30 percent with type 2 diabetes had a hospital admission during one year; patients with higher values for glycated hemoglobin (A1C) were at highest risk for admission [2]. The prevalence of diabetes rises with increasing age, as does the prevalence of other diseases; both factors increase the likelihood that an older person admitted to a hospital will have diabetes.

The treatment of patients with diabetes who are admitted to the general medical wards of the hospital for a procedure or intercurrent illness is reviewed here. The treatment of hyperglycemia in critically ill patients, the perioperative management of diabetes, and the treatment of complications of the diabetes itself, such as diabetic ketoacidosis, are discussed separately. (See "Glycemic control in critically ill adult and pediatric patients" and "Perioperative management of blood glucose in adults with diabetes mellitus" and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment" and "Hypoglycemia in adults with diabetes mellitus".)

The main goals in patients with diabetes needing hospitalization are to minimize disruption of the metabolic state, prevent adverse glycemic events (especially hypoglycemia), return the patient to a stable glycemic balance as quickly as possible, and ensure a smooth transition to outpatient care. These goals are not always easy to achieve. On the one hand, the stress of the acute illness tends to raise blood glucose concentrations. On the other hand, the anorexia that often accompanies illness or the need for fasting before procedures tend to do the opposite. Because the net effect of these countervailing forces is not easily predictable in a given patient, the target blood glucose concentration should generally be higher than in the outpatient setting.

Uncertainty regarding goal blood glucose concentration is compounded by the paucity of high-quality controlled trials on the benefits and risks of "loose" or "tight" glycemic management in hospitalized patients, with the exception of patients who are critically ill. (See "Glycemic control in critically ill adult and pediatric patients".)

In general, the goals are to:

- Avoid hypoglycemia
- Avoid severe hyperglycemia, volume depletion, and electrolyte losses
- Ensure adequate nutrition
- Assess patient educational needs and address informational deficiencies
- Ensure appropriate glucose management upon discharge until patient can be seen by the clinician managing his or her diabetes as an outpatient

Critical to achieving these goals is the frequent measurement of glucose, often in capillary blood, with a method that is known to be reliable. (See "Glucose monitoring in the ambulatory management of nonpregnant adults with diabetes mellitus", section on 'BGM systems'.)

**Avoidance of hypoglycemia** — Hypoglycemia should be avoided if at all possible. Measures to reduce the risk of hypoglycemia include:

- Adequate reduction in antihyperglycemic therapy when caloric intake is stopped or reduced.
- Avoidance of standard "sliding scale" of insulin without consideration of the patient's specific circumstances.
- Avoidance of overly aggressive attempts to provide "tight" glycemic management intraoperatively [3] or with intensive insulin therapy in critically ill patients [4]. (See "Glycemic control in critically ill adult and pediatric patients".)

Although relatively brief and mild hypoglycemia does not usually have clinically significant sequelae, hospitalized patients are particularly vulnerable to severe, prolonged hypoglycemia since they may be unable to sense or respond to the early warning signs and symptoms of low blood glucose.

Hypoglycemia (ie, serum glucose concentration <70 mg/dL [3.9 mmol/L]) can be harmful due to the effects of counterregulatory hormones, especially catecholamines, which may possibly induce arrhythmias and other cardiac events. This is especially true in older adults and those with preexisting ischemic heart disease. If the blood glucose falls to or below 54 mg/dL (3.0 mmol/L, termed "clinically significant hypoglycemia"), cognitive deficits may also ensue, which can lead to falls or aspiration. In a retrospective cohort study of over 2500 patients with diabetes hospitalized in the general wards, inpatient mortality was significantly higher for patients with at least one hypoglycemic (≤50 mg/dL [2.8 mmol/L]) episode [5].

**Avoidance of hyperglycemia** — Serious hyperglycemia should be avoided (see 'Prevention and treatment of hyperglycemia' below). Hyperglycemia can lead to volume and electrolyte disturbances mediated by osmotic diuresis and may also result in caloric and protein losses in under-insulinized patients.

Whether or not hyperglycemia imposes an independent risk for infection is a controversial issue. It is a longstanding clinical observation that patients with diabetes are more susceptible to infection [6]. Furthermore, immune and neutrophil function are impaired during marked hyperglycemia. Most of the studies addressing this question have focused on the risk of postoperative infection (and especially sternal wound infection) following coronary artery bypass grafting (CABG), and they show mixed results. This issue is discussed in detail elsewhere. (See "Susceptibility to infections in persons with diabetes mellitus", section on 'Risk of infection'.)

**Glycemic targets** — Although there are adequate experimental and observational data to recommend avoidance of marked hyperglycemia in patients with or at risk for infection, the precise glycemic target or threshold for noncritically ill or critically ill patients with preexisting diabetes mellitus has not been firmly established [6-8]. In the absence of data from clinical trials, the optimal blood glucose goal for hospitalized patients can only be approximate.

**Noncritically ill** — For most noncritically ill hospitalized patients with diabetes, we suggest a preprandial blood glucose target <140 mg/dL (7.8 mmol/L) with all random glucose values <180 mg/dL (10 mmol/L).

These targets are similar to those from a consensus statement by the American Diabetes Association (ADA; 140 to 180 mg/dL) and the clinical practice guideline of the Endocrine Society

[9,10]. The ADA has not stipulated any differences in target glucose values based on the timing of the measurements, such as preprandial versus postprandial. The Endocrine Society recommends pre-meal targets <140 mg/dL and "random" glucose levels <180 mg/dL. More stringent goals may be appropriate for stable patients with previous good glycemic management, and the goal should be set somewhat higher for older patients and those with severe comorbidities where the heightened risk of hypoglycemia may outweigh any potential benefit.

A reasonable glycemic goal to avoid hypoglycemia is to achieve fasting blood glucose concentrations no lower than 90 to 100 mg/dL (5.0 to 5.6 mmol/L); this will usually provide an adequate "cushion" in case the concentration falls further as the patient's illness improves. In general, all glucose levels should be kept below the 180 mg/dL (10.0 mmol/L) range to avoid further escalations, which may lead to dehydration, glycosuria, caloric loss, and increased risk of infection or hyperglycemic emergencies.

**Critically ill** — For the majority of critically ill patients, we agree with ADA recommendations for a blood glucose target of 140 to 180 mg/dL (7.8 to 10.0 mmol/L) [10]. Achieving this goal will usually require an insulin infusion, which should be initiated for persistent hyperglycemia ≥180 mg/dL (10.0 mmol/L). The data supporting these glycemic goals are presented separately. (See "Glycemic control in critically ill adult and pediatric patients".)

**Acute MI** — There is increasing evidence that suboptimal glycemic management in patients with diabetes (or stress-induced hyperglycemia in patients without diabetes) is associated with worse outcomes after acute myocardial infarction (MI) and that better glycemic management may be beneficial in some individuals.

#### PREVENTION AND TREATMENT OF HYPERGLYCEMIA

Treatment of hyperglycemia in hospitalized patients depends upon the type of diabetes, the patient's current blood glucose concentrations, prior treatment, the clinically assessed severity of illness, and the expected caloric intake during the acute episode ( algorithm 1 and algorithm 2) [1,11-13].

In the absence of large controlled clinical trials regarding how best to manage the inpatient with diabetes, the management approach outlined below is based primarily upon clinical expertise.

**Blood glucose monitoring** — At the time of admission or before an outpatient procedure or treatment, blood glucose should be measured and the result known. In addition, glucose

monitoring should be continued so that appropriate action may be taken.

- Frequency of monitoring The frequency of measurement depends upon the patient's status, the results of earlier measurements, and the steps taken as a result of those measurements. Importantly, in patients with diabetes (or hyperglycemia) who are eating, the blood glucose monitoring should occur just before the meal. In those who are receiving nothing by mouth, or receiving continuous tube feeds or total parenteral nutrition, the blood glucose monitoring should occur at regular, fixed intervals, usually every six hours.
- Mode of monitoring In hospitalized patients, blood glucose monitoring is typically performed through conventional capillary glucose testing with a fingerstick and glucose meter. Although continuous glucose monitoring (CGM) is not generally recommended for the inpatient or critical care setting, it has been used in inpatient locations more frequently since the onset of the coronavirus 2019 (COVID-19) pandemic. (See "COVID-19: Issues related to diabetes mellitus in adults".)

Clinical trial data generally have shown small and perhaps not clinically meaningful glycemic benefits with CGM compared with traditional glucose monitoring [14,15]. As an example, in a trial in 185 hospitalized adults with type 1 and type 2 diabetes on general medicine and surgery services, time spent in target glucose range (70 to 180 mg/dL [3.9 to 10 mmol/L]) and mean daily glucose did not differ between participants randomly assigned to glucose monitoring with CGM and those who underwent conventional monitoring [14]. The same study showed a small reduction in hypoglycemia reoccurrence with CGM compared with conventional monitoring, but the overall rates were very low [14]. CGM may be useful in selected inpatients, such as those for whom close contact with inpatient providers should be minimized (eg, COVID-19 or other highly transmissible infection) or possibly, in patients at high risk for hypoglycemia [14,16]. Hospitals that use these devices routinely must provide proper personnel training and resources for safe application of CGM [17].

It is certainly reasonable for patients using CGM at home to continue wearing these devices while hospitalized, as long as they maintain the required dexterity, vision, and cognitive capacity to safely implement such technology [17]. Any concerning glycemic data should be shared with the health care team for both confirmation and potential intervention. Most hospitals, however, have policies that forbid use of a patient's personal CGM data as the sole tool for glucose monitoring or to guide glucose management strategies, such as insulin administration.

# **Insulin delivery**

Basal-bolus (or basal-nutritional) insulin regimens — Although most patients will have type 2 diabetes, many will require at least temporary insulin therapy during inpatient admissions. In such patients, insulin may be given subcutaneously with an intermediate-acting insulin, such as neutral protamine hagedorn (human NPH), or a long-acting (basal) insulin analog, such as glargine, detemir, or degludec combined with a pre-meal rapid-acting insulin analog (lispro, aspart, glulisine) in patients who are eating regular meals (ie, a so-called "basal-bolus" regimen) ( algorithm 1 and algorithm 2). Short-acting (human regular) has fallen out of favor for meal-time dosing in the hospital, although there are no good studies comparing its efficacy or safety to the more costly rapid acting analogs.

**Sliding-scale insulin** — We do not endorse the routine use of regular insulin "sliding scales," particularly when prolonged over the course of a hospitalization. It has no role when used alone in those with type 1 diabetes, who always require basal insulin, even when receiving nothing by mouth. In type 2 diabetes patients who are very insulin deficient (typically insulin-treated older individuals, often but not always lean, with longstanding disease and a history of labile glucoses), the same recommendations apply.

However, in the usual patient with type 2 diabetes managed with oral agents or injectable glucagon-like peptide 1 (GLP-1)-based therapies, and whose glucose management on admission appears at goal, the temporary use of a sliding scale is reasonable for just one to two days as the trajectory of the patient's glycemia becomes apparent (see 'Correction insulin' below). However, after this period of time, a decision should be made about the need for a more physiological glucose management strategy for the remainder of the hospitalization ( algorithm 1 and algorithm 2).

The widespread use of sliding scales for insulin administration for hospitalized patients began during the era of urine glucose testing, and it increased after the introduction of rapid capillary blood glucose testing in the last two to three decades. However, there are few data to support its benefit and some evidence of potential harm when such treatment is applied in a rote fashion, that is, when all patients receive the same orders and, importantly, when the sole form of insulin administered is rapid-acting insulin every four to six hours without underlying provision of basal insulin.

This was illustrated in an observational study of 171 patients with diabetes who were admitted to a university hospital, 130 of whom (76 percent) were placed on a sliding-scale insulin regimen [18]. Sliding-scale insulin regimens when administered alone were associated with a threefold higher risk of hyperglycemic episodes as compared with no therapy (relative risk [RR] 2.85 for

"aggressive" scales, beginning at blood glucose 150 mg/dL [8.3 mmol/L] and 3.25 for "conservative" scales, beginning at blood glucose 200 mg/dL [11.1 mmol/L; p<0.05]). Thus, in this observational study, the use of sliding-scale insulin alone provided no benefit.

Correction insulin — Varying doses of rapid-acting insulin can be added to usual pre-meal rapid-acting insulin in patients on basal-bolus regimens to correct pre-meal glucose excursions. In this setting, the additional insulin is referred to as "correction insulin" ( algorithm 1 and algorithm 2), which differs from a sliding scale because it is added to planned mealtime doses to correct for pre-meal hyperglycemia. Correction dosing typically starts when the pre-meal blood glucose is ≥150 mg/dL (8.3 mmol/L). The dose of correction insulin should be individualized based upon relevant patient characteristics, such as previous glycemia, previous insulin requirements, and, if possible, the carbohydrate content of meals. When administered prior to meals, the type of correction insulin (eg, short acting or rapid acting) should be the same as the usual pre-meal insulin.

Meal-time correction insulin alone is sometimes used in place of a fixed mealtime dose, usually when risk of hypoglycemia is high, dietary intake is uncertain, or other clinical circumstance that warrants a conservative approach to glycemic management. Correction insulin alone may also be used as initial insulin therapy or as a dose-finding strategy in hyperglycemic patients with type 2 diabetes previously treated at home with diet or non-insulin agents who will not be eating regularly during the hospitalization. This use of correction insulin is essentially a "sliding scale." In fasting patients, a short-acting (ie, regular) insulin is typically administered every six hours ( algorithm 2). Rapid-acting insulin analogs can also be used but may require more frequent dosing (up to every four hours) and do not have clear advantage over regular insulin in fasting patients. Short-acting insulin can be given at bedtime in more modest doses to correct marked hyperglycemia (>250 to 300 mg/dL [16.6 mmol/L]). However, if the patient is eating and fingerstick glucose values are consistently elevated (>180 mg/dL [10.0 mmol/L]), a combination of intermediate- or long-acting insulin and pre-meal rapid-acting insulin (ie, a basal-bolus regimen) should be initiated ( algorithm 1).

Insulin infusion — Most patients with type 1 or type 2 diabetes admitted to the general medical wards can be treated with subcutaneous insulin. However, some practitioners institute intravenous insulin therapy (human regular insulin in solution) in certain circumstances, such as those with marked hyperglycemia (blood glucose >300 to 350 mg/dL [>16.7 to 19.4 mmol/L]) or in type 1 diabetes, especially those undergoing long and difficult surgery or those who will be expected to have significantly curtailed oral nutritional intake for several days postoperatively. There are little data showing that intravenous insulin is superior to subcutaneous insulin. The key point is that the patient should have at least a small amount of insulin circulating at all

times, which will significantly increase the likelihood of successfully managing blood glucose levels during illness.

In addition, the safe implementation of insulin infusion protocols requires frequent monitoring of blood glucose, which is not typically available on a general medical ward. Practical considerations including skill and availability of the nursing staff may impact the choice of delivery; complex intravenous regimens may be dangerous where nurses are short staffed or inexperienced. Thus, insulin infusions are typically used in critically ill intensive care unit (ICU) patients, rather than in patients on the general medical wards of the hospital.

There is a lack of consensus on how to best deliver intravenous insulin infusions, and individual patients may require different strategies. The best protocols take into account not only the prevailing blood glucose, but also its rate of change and the current insulin infusion rate. Several published insulin infusion protocols appear to be both safe and effective, with low rates of hypoglycemia, although most have been validated only in the ICU setting, where the nurse-to-patient ratio is higher than on the general medical and surgical wards [13,19,20]. There are few published reports on such protocols outside of the critical care setting. Computerized and web-based versions of several protocols are in widespread use, but they usually incur additional costs when proprietary devices/software are implemented [21,22]. (See "Glycemic control in critically ill adult and pediatric patients".)

In the course of giving an intravenous regular insulin infusion, we recommend starting with approximately half the patient's usual total daily insulin dose, divided into hourly increments until the trend of blood glucose values is known, and then adjusting the dose accordingly. A reasonable regimen usually involves a continuous insulin infusion at a rate of 1 to 5 units of regular insulin per hour; within this range, the dose of insulin is increased or decreased based on frequently measured glucose concentrations, ideally through the use of an approved protocol. In patients who are not eating, concomitant glucose infusion is necessary to provide some calories, reduce protein loss, and decrease the risk of hypoglycemia; separate infusions allow for more flexible management.

When the patient receiving intravenous insulin is more stable and the intercurrent event has passed, the prior insulin regimen can be resumed, assuming that it was effective in achieving glycemic goals. Because of the short half-life of intravenous regular insulin, the first dose of subcutaneous insulin must be given before discontinuation of the intravenous insulin infusion. If intermediate- or long-acting insulin is used, it should be given two to three hours prior to discontinuation, whereas short- or rapid-acting insulin should be given one to two hours prior to stopping the infusion.

**Patients with type 2 diabetes** — The treatment of patients with type 2 diabetes depends upon previous therapy and the prevailing blood glucose concentrations. Any patient who takes insulin before hospitalization should receive insulin throughout the admission ( algorithm 1 and algorithm 2) [13].

For a patient with reasonable glycemic management (A1C ≤8 percent) at home with diet or an non-insulin agent(s), initial correction insulin alone with meals (varying doses of rapid-acting insulin) is a reasonable initial treatment strategy (see 'Correction insulin' above). If the patient is unable to eat normally, oral agents (or injectable GLP-1-based therapies) should be discontinued. In patients who are eating and who do not have contraindications to their oral agent, oral agents (or injectable GLP-1-based therapies) may be cautiously continued if they are on the hospital's formulary (see 'Patients treated with oral agents or injectable GLP-1-based therapies' below). However, if contraindications develop or if blood glucoses are persistently elevated (>180 mg/dL [10.0 mmol/L]), these drugs should be discontinued and a more formal and comprehensive insulin regimen prescribed ( algorithm 1 and algorithm 2). Therapy should be returned to the patient's previous regimen (assuming that it had been effective) as soon as possible after the acute episode, usually as soon as the patient has resumed eating his or her usual diet. In those with elevated A1C upon admission, the discharge regimen should be modified to improve glycemic management, or at the very least, the patient should be evaluated by the clinician managing his or her diabetes soon (within several weeks) after discharge.

**Diet-treated patients** — Patients with type 2 diabetes treated by diet alone who are to have minor surgery or an imaging procedure, or who have a noncritical acute illness that is expected to be short lived, will typically need no specific antihyperglycemic therapy. Nevertheless, regular blood glucose monitoring is warranted to identify serious hyperglycemia, especially if steroid therapy is administered. The measurement system used should be standardized to ensure reasonable accuracy and precision. (See 'Blood glucose monitoring' above.)

Insulin therapy should be instituted if the preprandial blood glucose concentration is persistently ≥180 mg/dL (10 mmol/L), but the patient should be informed that insulin may not be necessary after the episode is over [10].

In patients who are not eating, correction insulin (as regular human insulin) can be administered every six hours as a correction/sliding scale ( algorithm 2) (see 'Correction insulin' above). Correction insulin with rapid-acting analogs can also be used, but the dosing frequency may need to be every four hours, so the more cost-effective regular insulin is preferred. If substantial doses are required, adding basal insulin will improve glycemia and allow reduced the doses of regular insulin.

If the patient is eating and fingerstick glucose levels are consistently elevated (≥180 mg/dL [10.0 mmol/L]), a basal-bolus insulin regimen should be initiated. Insulin requirements can be estimated based upon a patient's body weight ( algorithm 1). Alternatively, requirements can be based upon the total number of units of correction insulin administered over the course of a hospital day. Approximately 50 percent of the total daily dose can be given as basal insulin, and the remaining approximately 50 percent can be given in equally divided doses prior to meals (one-third prior to each meal).

Patients treated with oral agents or injectable GLP-1-based therapies — In general, insulin is the preferred treatment for hyperglycemia in hospitalized patients previously treated with oral agents (or injectable glucagon-like peptide 1 [GLP-1]-based therapies). This approach stems from the fact that insulin doses can be rapidly adjusted and, therefore, can quickly correct worsening hyperglycemia. In addition, noninsulin diabetes therapies have not been widely tested in the hospital setting. However, there are some circumstances where insulin may not be necessary. As an example, in patients who are well managed on their outpatient regimen, who are eating, and in whom no change in their medical condition or nutritional intake is anticipated, oral agents may be continued, as long as new contraindications are neither present nor anticipated during the hospital admission, and as long as the medications (or similar brands) are on the hospital formulary. Of note, injectable GLP-1-based therapies are expensive and often not on hospital formularies; their use in the hospital setting is therefore uncommon.

If a patient was previously eating but is unable to eat after the evening meal in preparation for a procedure the next morning, oral antihyperglycemic drugs should be omitted on the day of a procedure (surgical or diagnostic). If procedures are arranged as early in the day as possible, antihyperglycemic therapy and food intake can simply then be shifted to later in the day.

If the illness requiring admission is more severe (eg, an infection requiring hospitalization), hyperglycemia is more likely, even when there is decreased food intake, and most acutely ill patients will need insulin. In this setting, oral agents should be discontinued. Overt hyperglycemia (≥180 mg/dL [10.0 mmol/L]) in patients previously treated with oral agents who are not eating can be treated briefly with intermittent, subcutaneous doses of regular (every six hours) or rapid-acting (every four to six hours) insulin, provided the blood glucose is not severely elevated, responds well to the insulin, and the problem lasts only a day or two at most (see 'Correction insulin' above). If eating, rapid-acting insulin is preferred, administered before meals. However, a more formal and comprehensive insulin regimen, including some form of basal insulin, is usually preferred when hyperglycemia persists ( algorithm 1 and algorithm 2).

Oral agents should generally not be administered to patients who are not eating. In addition, many oral agents have specific contraindications that may emerge in hospitalized patients:

- Metformin Metformin is contraindicated in situations in which kidney function and/or hemodynamic status is either impaired or threatened, due to the increased risk of lactic acidosis. Examples include patients with acute cardiac or pulmonary decompensation, acute kidney injury, dehydration, sepsis, urinary obstruction, or in those undergoing surgery or radiocontrast studies. Given the typical case mix in most acute care hospitals, metformin should probably be discontinued at least temporarily in most patients. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)
- **DPP-4 inhibitors** Dipeptidyl peptidase 4 (DPP-4) inhibitors (eg, sitagliptin, saxagliptin, linagliptin, alogliptin) exert their effect mainly in the postprandial setting. As a result, they have an uncertain role in patients who are not eating. DPP-4 inhibitors have not been used or studied extensively in the acute care setting [23]. Two studies suggested that they may be reasonably effective in mildly hyperglycemic patients with type 2 diabetes who are eating [23,24]. We tend to continue them as they may modestly reduce hyperglycemia and decrease the need for insulin injections. They also have few contraindications or safety concerns, and DPP-4 inhibitors do not increase the risk of hypoglycemia. All DPP-4 inhibitors except linagliptin require dose reduction in the setting of impaired kidney function. (See "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Dosing'.)
- **Sulfonylureas** Sulfonylureas (eg, glyburide, glipizide, glimepiride) are associated with hypoglycemia that can be severe and prolonged. Although they may be continued during the hospitalization in stable patients who are expected to eat regularly, unexpected alterations in meal intake will increase the risk for hypoglycemia.
  - On balance, sulfonylureas should usually be discontinued, at least temporarily, in the hospitalized patient. (See "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects'.)
- Meglitinides Non-sulfonylurea secretagogues (meglitinides [eg, repaglinide, nateglinide]) work similarly to the sulfonylureas but have a shorter duration of action. As a result, these prandial-administered drugs may have a theoretical advantage in hospitalized patients but should also be used cautiously, including in those with acute ischemic heart disease events. Further limiting their inpatient use, meglitinides are

typically not on hospital formularies. (See "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus".)

- **GLP-1-based therapies** GLP-1-based therapies (eg, exenatide, liraglutide, lixisenatide [limited availability], dulaglutide, semaglutide, tirzepatide) may result in nausea and decreased calorie intake and are more effective for postprandial glucose management. As a result, their use should generally be avoided in the acute setting. They are also not usually included on most hospital formularies, in part due to high cost. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Introduction'.)
- SGLT2 inhibitors Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, dapagliflozin, canagliflozin, empagliflozin) promote the renal excretion of glucose. They increase calorie losses as well as risk of dehydration, volume contraction, and genitourinary tract infections. In addition, euglycemic diabetic ketoacidosis has been reported in patients with both type 1 (during off-label use) and, more rarely, type 2 diabetes who were taking SGLT2 inhibitors. These drugs should therefore generally not be used in the inpatient setting, particularly when patients are acutely ill, although they may be started just prior to discharge if compelling indications are present. For example, these agents may be used by cardiologists and especially heart failure specialists for the benefit of SGLT2 inhibitors in the setting of heart failure. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Adverse effects' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Sodium-glucose co-transporter 2 inhibitors' and "Treatment and prognosis of heart failure with preserved ejection fraction", section on 'Sodium-glucose co-transporter 2 inhibitors'.)
- Thiazolidinediones The thiazolidinediones (eg, pioglitazone, rosiglitazone) are associated with peripheral edema and should be avoided in patients with heart failure. If the question of ventricular dysfunction is raised during a hospitalization, thiazolidinediones should be held until the situation is clarified. The antihyperglycemic effect of this drug class extends for several weeks after discontinuation (as does the fluid-retaining effect), so that temporary interruption of therapy should have little effect on glycemia. (See "Thiazolidinediones in the treatment of type 2 diabetes mellitus".)
- **Alpha-glucosidase inhibitors** Alpha-glucosidase inhibitors (eg, acarbose, miglitol) are generally used infrequently and are not typically on hospital formularies. Moreover, these inhibitors of intestinal carbohydrate absorption are only effective in patients who are

eating and therefore have a limited role in this setting. (See "Alpha-glucosidase inhibitors for treatment of diabetes mellitus".)

**Patients treated with insulin** — Insulin therapy should be continued in all patients already taking it to maintain a reasonably constant basal level of circulating insulin. Failing this, severe hyperglycemia or even ketoacidosis can occur, even in patients labeled as having type 2 diabetes but who have become significantly insulin deficient over a prolonged disease course.

• Basal-bolus (or basal-nutritional) regimens – In the non-acute hospital setting and when the patient is eating regularly, basal insulin (NPH or detemir twice daily or glargine, detemir, or degludec once daily [or nightly]) in combination with short- or rapid-acting prandial (bolus) insulin (regular, lispro, aspart, glulisine) is generally effective for patients receiving insulin at home or for patients with poorly regulated blood glucose previously managed with diet or oral agents ( algorithm 1).

If the glucose was well managed with the outpatient insulin regimen, we typically reduce the dose by 25 to 50 percent because, in the more controlled environment of the hospital (where the amount of food consumed may be less than at home and blood glucose levels are checked regularly), patients may need considerably less insulin than they were taking in the outpatient setting. However, clinicians should be ready to rapidly advance the dose if this reduction results in inadequate glycemic management.

Different basal-bolus regimens are similarly effective in reducing A1C concentrations when insulin doses are titrated to achieve glycemic goals. As an example, in a trial of detemir/aspart versus NPH/regular in 130 hospitalized patients, there was no difference in glycemic management or frequency of hypoglycemia between the two regimens [25].

In some studies, treatment with such a basal-bolus insulin regimen was associated with better glycemic outcomes than sliding-scale insulin [26-29]. As an example, in one open-label, randomized trial of insulin glargine supplemented with preprandial glulisine versus sliding-scale insulin, a greater proportion of patients treated with the basal-bolus regimen achieved target glucose values (66 versus 38 percent, respectively) [26]. However, in this study, the mean daily dose of insulin was more than threefold higher in the basal-bolus-treated patients than in those assigned to sliding scale, likely reflecting a failure to titrate the doses of sliding-scale insulin. In some [28,29], but not all [26,27], trials, better glycemic management with basal-bolus versus sliding-scale insulin was associated with more hypoglycemia (glucose <70 mg/dL [3.9 mmol/L] in 23.1 and 4.7 percent of patients, respectively, and <40 mg/dL [2.2 mmol/L] in 3.8 and 0 percent, respectively).

• **U-500 insulin** – Patients treated with U-500 regular insulin at home may continue U-500 (with a 50 percent dose reduction since glucose values often improve substantially in the hospital in patients previously requiring large doses of insulin at home, due to more restrictive hospital diets), if it is available from the hospital formulary. Because the high concentration of insulin delays absorption, the pharmacologic profile of U-500 regular insulin is most similar to that of NPH [30]. Thus, if U-500 is not available, U-100 NPH insulin twice daily should be substituted (again, with a 50 percent dose reduction).

We would also caution that errors are common with U-500 administration, and clear communication among patient, clinician, nursing staff, and pharmacy is imperative to ensure proper dosing. Although in the past U-500 insulin was dispensed using standard U-100 insulin or Tuberculin syringes, a dedicated U-500 insulin syringe is available and U-500 insulin should be dispensed with the U-500 insulin syringe, if possible [31]. The syringe contains scale markings from 25 to 250 units in 5-unit increments (total volume 0.5 mL). The insulin dose should be expressed in units, rather than in volumetric terms as was the convention with the Tuberculin or U-100 syringes. U-500 insulin syringes are not available with a safety needle and, therefore, may not be allowed in some facilities. In such cases, the U-500 insulin pen device may be used. The pen dosing window shows the number of units of U-500 to be injected, and the pen delivers the volume that corresponds to the selected dose. The pen contains 1500 units (500 units/mL) of insulin.

If neither dedicated U-500 insulin syringes nor the U-500 insulin pen device is available, U-500 insulin can be dispensed using a Tuberculin syringe, rather than a U-100 insulin syringe, to emphasize that it is different from U-100 regular insulin. With the Tuberculin syringe, every 0.1 mL would equal 50 units of insulin. The obvious concern when using U-500 insulin with a Tuberculin syringe is the potential for confusion of volume and units. For institutions using Tuberculin syringes to deliver U-500 insulin, therefore, U-500 insulin should be dispensed directly from the hospital pharmacy, in individually labelled Tuberculin syringes.

• **Insulin pump** – In patients with type 2 diabetes already using an insulin pump, pump therapy may be continued in the hospital so long as certain criteria are met for safe implementation. (See 'Patients with type 1 diabetes' below.)

Automated insulin delivery (AID) systems are typically used in the outpatient setting, more often in patients with type 1 diabetes. In a short-term trial comparing an AID system with conventional subcutaneous insulin therapy in hospitalized patients (noncritical care) with type 2 diabetes, a greater proportion of patients receiving AID were in the target range of 100 to 180 mg/dL (5.6 to 10 mmol/L; 65.8 versus 41.5 percent) [32]. Mean glucose level was

lower with AID (154 versus 188 mg/dL in the control group [8.5 versus 10.4 mmol/L]), but there was no significant difference in duration of hypoglycemia or in the amount of insulin delivered. Whether the modest improvement in glycemia in noncritical hospitalized patients improves outcomes and warrants the potential increased cost is uncertain. (See "Continuous subcutaneous insulin infusion (insulin pump)", section on 'Types of insulin pumps'.)

• Reduced or absent oral intake – When food intake is diminished or stopped completely in a patient treated with insulin (eg, in preparation for surgery or other procedures), planned pre-meal rapid-acting insulin is discontinued, and the dose of intermediate- or long-acting insulin is reduced. If an episode is clearly short lived (eg, a procedure done in the early morning), subcutaneous insulin (usual dose of short acting and intermediate or long acting) and breakfast can simply be delayed until after the episode. The adjustment of insulin doses in preparation for surgery or other procedures is reviewed in more detail separately. (See "Perioperative management of blood glucose in adults with diabetes mellitus", section on 'Insulin injection'.)

Once the patient is taking a normal diet, the usual at-home regimen can be restarted, as long as glycemic goals were being met. If altered nutritional intake is present, reduced doses of insulin will be required, starting with doses similar to those administered in the preprocedure setting.

**Patients with type 1 diabetes** — Patients with type 1 diabetes have an absolute requirement for insulin at **all times**, whether or not they are eating, to prevent ketosis. The doses of insulin needed are usually lower than in patients with type 2 diabetes since most of the former do not have insulin resistance. However, their blood glucose concentrations tend to fluctuate more during the course of the illness or procedure. It is important to avoid hypoglycemia, even if the consequence is a temporary modest rise in the blood glucose concentration.

Insulin can be given either subcutaneously or intravenously. Algorithms for glycemic management of nonfasting and fasting patients with type 1 diabetes who are not critically ill are shown for subcutaneous dosing regimens ( algorithm 1 and algorithm 2) [13].

If the patient is receiving nothing by mouth, the administration of basal insulin is still required. As examples:

• **Patients using an insulin pump** – For a patient treated with a continuous insulin infusion via a pump, the basal insulin can be continued at the usual rate, or the overnight basal rate may be reduced by 20 percent to minimize the risk of hypoglycemia the next morning. No boluses would be administered until the patient is able to eat. Since nursing staff are

not always familiar or comfortable with the use of insulin pumps, patients should be alert enough to manage their pump therapy and possess sufficient vision and dexterity to safely use the device. In addition, vigilance regarding pump catheter placement is necessary. Catheters may inadvertently be dislodged during transfers in the operating room or in bed, and if the patient is not alert enough to provide self-care, the health care providers should consider changing to conventional injection therapy until the patient is able to manage pump therapy again.

• Patients treated with multiple daily insulin injections – For a patient who usually takes 20 units of glargine every evening and rapid-acting insulin before each meal (dose based upon pre-meal blood glucose and carbohydrate content of meal), the usual dose of glargine can be continued. In patients with tightly managed glycemia, an alternative approach is to reduce the dose of glargine by 10 to 20 percent (eg, give 16 to 18 units) to minimize the risk of hypoglycemia that might require oral ingestion of calories and thereby delay the planned procedure. Short-acting insulin should not be given, unless significant hyperglycemia is noted, as described above.

For a patient who usually takes 24 units of NPH and 4 units of regular insulin in the morning, one-half to two-thirds (12 to 16 units) of the usual morning dose of NPH insulin can be given (if the morning blood glucose value is not too low, ie, is at least 120 mg/dL [6.7 mmol/L]). Short- or rapid-acting insulin should not be given, except if significant hyperglycemia (>200 to 250 mg/dL [11.1 to 13.9 mmol/L]) is found in the morning. In such cases, only small doses (1 to 4 units) should be given with the goals of reducing the blood glucose level to <180 mg/dL (10 mmol/L) and avoiding hypoglycemia during the ongoing fast.

Blood glucose should be measured every two to three hours until the first meal is eaten. Small amounts of short- or rapid-acting insulin can be administered every four to six hours to correct hyperglycemia (ie, glucose >150 to 200 mg/dL [8.3 to 11.1 mmol/L]). Intravenous glucose (at approximately 3.75 to 5 g/hour, eg, 5 percent dextrose at 75 to 100 mL per hour) should be given to limit the metabolic changes of starvation. (See "Cases illustrating intensive insulin therapy in special situations".)

**Patients receiving enteral or parenteral feedings** — Patients with diabetes who are receiving total parenteral nutrition (TPN) or tube feeds (bolus or continuous) require special consideration.

**TPN** — In patients receiving total parenteral nutrition (TPN), insulin may be administered as part of the nutritional solution, if allowed by the hospital pharmacy. To determine the correct

dose of insulin to add to the TPN fluid, a separate infusion of regular insulin can be used initially. When glucoses have reached goal, the total daily dose of regular insulin provided by the insulin drip is calculated; 80 percent of this amount is added to the TPN fluid as regular insulin to be delivered over 24 hours. For example, if the intravenous insulin infusion at steady state was set at 1 unit per hour (or 24 units per day), around 80 percent of this amount (20 units) should be added to the TPN solution by the pharmacy to be given over the course of the day. The amount of insulin can then be titrated every one to two days, based upon glucose monitoring. Since more frequent adjustments are impractical and costly, the concurrent use of rapid- or short-acting insulin as correction every six hours will help to fine-tune glycemic management. (See 'Correction insulin' above.)

If TPN is interrupted, most patients with type 2 diabetes can be followed with careful glucose monitoring. Insulin should be administered if hyperglycemia occurs. In patients with type 1 diabetes, hyperglycemia will occur and can result in ketosis if all insulin is withheld. Thus, patients with type 1 diabetes require insulin when the TPN is interrupted. The amount and type of insulin depend upon the anticipated duration of the interruption. Because of the potential for inadvertent discontinuation of insulin therapy if TPN is interrupted, some clinicians recommend giving a portion of the basal insulin as an injection (eg, 50 percent) in patients with type 1 diabetes. In the example above (patient receiving 24 units of regular insulin a day, 80 percent of this amount [19 units] added to the TPN solution), approximately 10 units of regular insulin can be added to the TPN solution and 9 units of NPH, glargine, or detemir administered as a basal injection. This approach can also be used in insulin-requiring patients with type 2 diabetes.

**Enteral feedings** — In patients receiving continuous enteral feeds, the total daily dose of insulin could be administered as basal insulin alone (once-daily glargine, detemir, or degludec, or twice-daily detemir or NPH). However, if the enteral feeds are unexpectedly discontinued, hypoglycemia may occur. Thus, a safer approach may be to administer approximately 50 percent of the total daily insulin dose as basal insulin and 50 percent as prandial (short- or rapid-acting) insulin, which is given every four (rapid-acting insulin) to six (short-acting insulin) hours [33]. A similar ratio of basal-to-prandial insulin can be used for patients receiving bolus feeds, for whom the prandial insulin would be divided equally before each bolus feed. Correction rapid- or short-acting insulin can then be administered, as needed, with the prandial insulin (same type). In those receiving cycled enteral feeding (eg, 8 to 10 hours overnight), the ideal insulin may be NPH, which has an activity profile similar to this duration, its effect waning when the feeds are stopped. Again, correction rapid- or short-acting insulin can then be administered as needed to optimize glycemic management. (See 'Correction insulin' above.)

Another approach is to use short-acting insulin alone. This approach is supported by the findings of a randomized trial of sliding-scale, regular insulin every four to six hours alone or in combination with insulin glargine in 50 noncritically ill patients with diabetes receiving enteral nutrition [34]. Insulin doses were adjusted daily based upon fingerstick blood glucose measurements, and NPH insulin was added in the sliding-scale, regular insulin group when glucose levels persistently exceeded 180 mg/dL (10 mmol/L). There were no differences in any glycemic measures (mean study glucose, mean peak or nadir glucose, hypoglycemia events, or total daily insulin dose) between the two groups. However, NPH insulin was required in 48 percent of subjects randomly assigned to sliding-scale, regular insulin. Thus, when sliding-scale, regular insulin alone is chosen as the initial management strategy for patients receiving enteral feeds, the addition of basal insulin is often required to maintain adequate glycemic management.

If the enteral feeds (continuous or bolus) are unexpectedly discontinued, an intravenous 10 percent dextrose solution, providing a similar number of carbohydrate calories as was being administered via the enteral feeds, should be infused in order to prevent hypoglycemia, especially if the blood glucose concentration falls below 100 mg/dL.

**Consultation** — Most of the time, the treatment of hyperglycemia in patients with diabetes in these stressful circumstances can be done by the patient's internist, generalist, or hospitalist. However, each clinician needs to decide whether or not the patient would benefit from additional advice; consultation with a diabetes specialist or endocrinologist may help, particularly if accompanied by a team including personnel who can provide patient education and nutritional advice. This team approach can decrease the patient's length of stay as well as decrease the total cost of care [35,36]. Using the hospitalization to enhance the patient's knowledge about the disease and to improve self-management is encouraged.

**Evaluation of overall care** — A brief hospitalization is an excellent opportunity to assess or reassess overall care in patients with diabetes. If appropriate, attention should be paid to preventive measures (such as smoking cessation, hypertension management, treatment of dyslipidemia, and appropriate vaccinations) [37], glycemic management, assessment of possible complications of diabetes, and overall patient education. This assessment should lead to the formulation of a plan for future treatment after the patient is discharged. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus".)

In type 2 diabetes, an insulin regimen may not be necessary after the illness requiring hospitalization has resolved. In addition, even when such a regimen is considered to be the ideal outpatient therapy upon discharge, the patient may not be able to comply safely with the prescribed insulin program, which requires a degree of education, commitment, and self-

discipline not exhibited by all. Thus, it is important to determine both the insulin needs as well as the self-care capacities of each patient prior to discharge. Optimal regimens should be individualized for each patient.

Patients may require a significant dose adjustment after discharge from the hospital, which is why clear communication between the clinician dealing with the acute illness and the clinician who will follow the patient's diabetes care after discharge is so important. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus".)

Patients found to be newly hyperglycemic during times of illness may actually have undiagnosed diabetes. A glycohemoglobin test (A1C) can help discriminate between acute, stress-related hyperglycemia and preexistent diabetes. At a minimum, these individuals should be retested as outpatients upon full recovery. Adequate patient education, discharge planning, and the important transition to the outpatient arena should be facilitated by the personnel dedicated to diabetes care at each institution.

#### **SOCIETY GUIDELINE LINKS**

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults" and "Society guideline links: Diabetes mellitus in children".)

#### SUMMARY AND RECOMMENDATIONS

- **General goals** The main goals in patients with diabetes needing hospitalization are to minimize disruption of the metabolic state, prevent adverse glycemic events (especially hypoglycemia), return the patient to a stable glycemic balance as quickly as possible, and ensure a smooth transition to outpatient care. (See 'Goals in the hospital setting' above.)
- Glycemic goals For most noncritically ill hospitalized patients with diabetes, we suggest
  a preprandial blood glucose target <140 mg/dL (7.8 mmol/L) with all random glucose
  values <180 mg/dL (10 mmol/L) (Grade 2C). (See 'Noncritically ill' above.)</li>

More stringent goals may be appropriate for stable patients with previous good glycemic management, and more conservative targets should be set for older patients and those with severe comorbidities where the heightened risk of hypoglycemia may outweigh any potential benefit.

# Type 2 diabetes

- Patients treated by diet alone usually need no specific antihyperglycemic therapy.
   Frequent blood glucose monitoring is warranted to prevent serious hyperglycemia from being unrecognized. (See 'Diet-treated patients' above.)
- Patients treated with oral antihyperglycemic drugs or injectable glucagon-like peptide 1
  (GLP-1)-based therapies can occasionally continue their usual drug regimen in some
  circumstances (patient eating, glucose well managed, and no contraindication to oral
  agents) ( algorithm 1). However, if blood glucose levels are poorly managed with the
  usual oral agents or if the patient is not eating, drug therapy should be discontinued
  and insulin initiated ( algorithm 2). (See 'Patients treated with oral agents or
  injectable GLP-1-based therapies' above.)
- Insulin therapy should be continued in all patients already taking it to maintain a
  reasonably constant basal level of circulating insulin ( algorithm 1 and
  algorithm 2). (See 'Patients treated with insulin' above.)

# Type 1 diabetes

- Patients with type 1 diabetes require insulin at all times, whether or not they are
  eating. Insulin can be given either subcutaneously or intravenously. For subcutaneous
  insulin, sliding scales should never be used as the sole insulin. Optimally, basal insulin
  (glargine, detemir, degludec, or neutral protamine hagedorn [NPH]) should be
  combined with prandial and correction insulin (typically, rapid-acting insulin)
  ( algorithm 1 and algorithm 2). (See 'Patients with type 1 diabetes' above.)
- When intravenous insulin is given, once the blood glucose levels are in goal range, glucose (as dextrose or in total parenteral nutrition [TPN]) should be administered to prevent catabolism. Blood glucose should be measured frequently (every one to two hours in patients receiving an insulin infusion). (See 'Insulin infusion' above.)

#### **ACKNOWLEDGMENT**

The UpToDate editorial staff acknowledges David McCulloch, MD, who contributed to earlier versions of this topic review.

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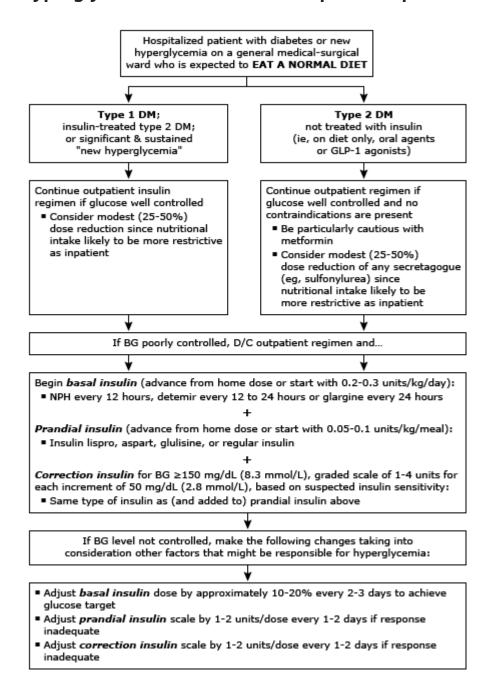
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# Hyperglycemia treatment for hospitalized patients eating a normal diet

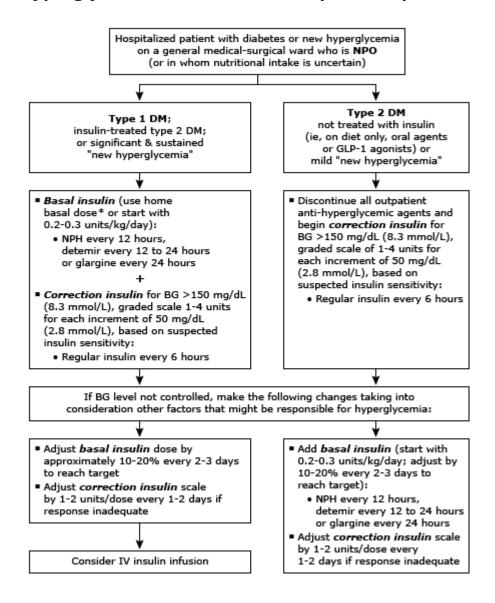


Proposed algorithm for management of diabetes and hyperglycemia in the noncritical care setting.

DM: diabetes mellitus; GLP-1: glucagon-like peptide-1; BG: blood glucose; D/C: discontinue.

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# Hyperglycemia treatment for hospitalized patients receiving nothing by mouth



Proposed algorithm for management of diabetes and hyperglycemia in the noncritical care setting.

NPO: nil per os (nothing by mouth); DM: diabetes mellitus: GLP-1: glucagon-like peptide-1; BG: blood glucose; IV: intravenous.

\* Adjusted based on current degree of hyperglycemia; consider modest (20-25%) dose reduction if tightly controlled on admission, to be conservative.

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