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Nutrition and Hyperglycemia Management in the Inpatient Setting (Meals on Demand, Parenteral, or Enteral Nutrition)

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Abstract
Purpose of Review The goal of this paper is to provide the latest evidence and expert recommendations for management of hospitalized patients with diabetes or hyperglycemia receiving enteral (EN), parenteral (PN) nutrition support or, those with unrestricted oral diet, consuming meals on demand.
Recent Findings Patients with and without diabetes mellitus commonly develop hyperglycemia while receiving EN or PN support, placing them at increased risk of adverse outcomes, including in-hospital mortality. Very little new evidence is available in the form of randomized controlled trials (RCT) to guide the glycemic management of these patients. Reduction in the dextrose concentration within parenteral nutrition as well as selection of an enteral formula that diminishes the carbohydrate exposure to a patient receiving enteral nutrition are common strategies utilized in practice. No specific insulin regimen has been shown to be superior in the management of patients receiving EN or PN nutrition support. For those receiving oral nutrition, new challenges have been introduced with the most recent practice allowing patients to eat meals on demand, leading to extreme variability in carbohydrate exposure and risk of hypo and hyperglycemia.
Summary Synchronization of nutrition delivery with the astute use of intravenous or subcutaneous insulin therapy to match the physiologic action of insulin in patients receiving nutritional support should be implemented to improve glycemic control in hospitalized patients. Further RCTs are needed to evaluate glycemic and other clinical outcomes of patients receiving nutritional support. For patients eating meals on demand, development of hospital guidelines and policies are needed, ensuring optimization and coordination of meal insulin delivery in order to facilitate patient safety.

Keywords Diabetes · Hospitalized patients · Specialized nutrition · Enteral nutrition · Parenteral nutrition · Meals on demand

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Introduction

Hyperglycemia is common in hospitalized patients and is associated with adverse outcomes. An insulin regimen with basal, nutritional, and correctional components is the preferred glycemic treatment strategy in patients with oral nutritional intake [1••]. Since postprandial blood sugars are largely influenced by carbohydrate intake, improved glycemic control cannot be accomplished without taking carbohydrate content into consideration when dosing insulin. Appropriate blood glucose control in the setting of nutritional coverage poses a particular challenge due to variable carbohydrate exposure related to patient issues (appetite, meals choices, and or tolerance) as well as

systems issues (unplanned interruptions in nutrition, delays in timing of prandial insulin administration, etc.) [2]. The contribution of nutritional intake, or lack thereof, to glycemic management in the hospital setting is significant yet there is paucity of published data to guide the management of these patients. Here, we have reviewed recent papers that are addressing therapeutic challenges of patients receiving meals on demand, parenteral nutrition (PN) and enteral nutrition (EN). We are providing recommendations for management of these patients based on published literature, as well as extensive personal clinical experience and have summarized recent consensus opinions from major national diabetes organizations.

Meals on Demand

While the popular concept of the "1800 cal ADA diet" continues to live in colloquial in-hospital terminology, the fact is that the American Diabetes association (ADA) does not recommend a specific type of a diet or macronutrient distribution [1••] and instead emphasizes the need for diet individualization based on specific patient needs and characteristics. In order to minimize variability in carbohydrate intake, many hospitals have introduced consistent carbohydrate (carb) diets, which provide a fixed amount of carbohydrate to match the fixed prandial insulin dose prescribed [2, 3]. However, poor time-matching of point-of-care (POC) glucose measurement, meal delivery, and nutritional insulin coverage still place patients at risk of hypo- or hyperglycemia. Even with a prescribed consistent carbohydrate diet, some patients are unable or unwilling to ingest all of their meal. For such patients, it is generally recommended to administer the prescribed bolus (rapid-acting) insulin after the patient eats, thus covering the ingested food by counting the actual consumed amount of carbohydrates [1••]. In lieu of carbohydrate counting, an alternative approach is to dose bolus insulin immediately after meals by administering half the dose when a patient consumes half of the meal, and to withhold the dose if less than half of the meal is consumed.

Some hospitals have moved over to what is frequently referred to as a "controlled" carbohydrate meal plan (a term that has not been clearly defined in the literature) where number of carbs are counted but the patient has flexibility to have different total carb content with each meal. The term "controlled" meal plan implies some form of carbohydrate limitation (control), but that has not been academically defined or empirically accepted. Some hospitals have chosen to limit the total amount of carbs on each meal tray, others have not.

Recently, there has been an emerging interest in patient amenities in-hospital care in an effort to improve patient satisfaction scores [4]. Many hospitals have transitioned from a consistent or controlled carbohydrate diet to "meals on demand" ("room service") granting patients flexibility in the timing of their meal as well as caloric/carbohydrate content of the food selected [2]. The hope is that "room service" may improve patient satisfaction, increase food quality while providing cost savings [5]. For patients with diabetes, "meals on demand" may increase the risk for adverse glycemic outcomes due to variability in the carbohydrate content of meals, impaired coordination of meal timing with POC blood glucose monitoring and prandial insulin coverage as well as the potential for stacking of insulin with frequent meal consumption.

Possible approaches to minimize dissatisfaction with standard consistent or controlled carbohydrate hospital diets and pressures for "meals on demand" service, while achieving safe and effective glycemic control are:

a) Replace former standard consistent carbohydrate diet with patient controlled consistent carbohydrate meal plan. This meal plan actually contains the same recommendation for carbohydrate content as the standard diet—however, instead of automatic computerized menu substitutions when meal selection do not fit into recommended plan, nutrition staff provides educational feedback to patient. In addition, menu content includes a broader variety of food choices, similar to those available outside of the hospital. Thus, a patient is educated on how to incorporate a consistent carbohydrate diet into their everyday nutritional choices. When the two dietary choices were compared, there was no difference in the self-care behavior with the consistent carbohydrate meal plan or mean BG but patient controlled group reported a greater patient satisfaction and had more opportunities for patient education [3].
b) Allow patients to order meals on demand, while administering prandial insulin based upon carbohydrate intake to account for carbohydrate variability. This practice requires time and resources for extensive training and education of all the staff involved. To date, only three relatively small studies have formally examined the use of carb counting in the hospital, and the results are mixed. The only study that showed improvement in mean BG with carb counting compared it to use of conventional sliding-scale (non-individualized correction scale of rapid-acting insulin starting at BG of 200 mg/dL) in a setting of inconsistent utilization of basal insulin [6]. The other two studies found that a fixed meal dosing strategy provided similar glucose control as flexible meal dosing [7, 8]. In a study by Dungan et al. where insulin was ordered by the diabetes management team, there were no in-between group differences in mean carbohydrate intake per meal consumed, frequency of hypoglycemia occurrence, or overall patient satisfaction [7]. A recent retrospective study by Thurber et al., evaluated glycemic control of hospitalized cardiology patients, and

found that postprandial glucose values were similar in both fixed and flexible prandial insulin treatment groups [8]. Total daily insulin doses (including prandial insulin) were also found to be comparable between the groups, but the carbohydrate content of the meals provided was not quantified. Glycemic management was provided by a diabetes consult service consisting of physicians, nurse practitioners, and physician assistants specializing in inpatient hyperglycemic management who had the freedom to choose fixed vs. carbohydrate based prandial insulin dosing. In summary, while inpatient dosing of insulin according to an insulin to carbohydrate ratio intuitively appears to be a solution for sustaining glycemic control in the setting of meals provided on demand, there are currently no large, high-quality studies showing the superiority of this approach compared to a standard basal-bolus-correction regimen. Furthermore, prandial insulin dosing using carbohydrate counting requires greater expertise of hospital staff in food service and nursing and creation of appropriate protocols needed for counting carbohydrates and safe administration of insulin regimens requiring complex calculations. This raises questions about the safety and feasibility of this practice in hospitals where such expanded nurse competencies may not be supported.

c) Develop guidelines to enhance coordination of care necessary for administration of meal related insulin dosing [2, 9]. An example of guidelines for promoting appropriate insulin administration for meals on demand, recently proposed by Korytkowski et al. [10] recommend that:

- Patients are able to order meals within regularly scheduled time intervals
- Nutrition services will call patient for any orders not placed within these intervals
- Personnel distributing meals alert the RN that a meal has been delivered to patient to prompt a BG check before the meal and insulin administration either pre or post meal.
- Prominent note is provided with meal to remind a patient to request a BG check and insulin dose prior to ingesting a meal
- Avoid administration of prandial insulin at intervals of <4 h to avoid "insulin stacking"

Notifying the bedside nurse that a meal has been ordered may reduce the likelihood that the patient starts eating before the nurse checks the blood glucose. A second notification is needed that the meal has arrived in case prandial insulin is ordered, although it could be as simple as turning on the call light when delivering the meal and showing the patient the note on the tray to wait for the nurse before eating. Special attention needs to be given to those patients with cognitive deficits or language barrier that preclude effective communication.

Hyperglycemia in Nutritional Support

Pathogenesis and Effects

Hyperglycemia is seen in up to 30% of patients receiving EN and more than half of patients receiving PN [11, 12••, 13, 14]. Contributing factors include increased hepatic glucose production, as well as reduced peripheral utilization caused by stress and increased levels of cytokines and stress hormones such as glucagon, cortisol, and catecholamine [15]. Excessive delivery of glucose and gluconeogenic substrates via enteral or parenteral routes in hospitalized patients also contributes to hyperglycemia. Adverse effects of hyperglycemia are well recognized and include deleterious effects on fluid balance (through glycosuria and dehydration), immune function, and inflammation [16, 17]. Acute hyperglycemia may also impair ischemic preconditioning, which is a protective mechanism for ischemic insult [18].

PN and Hyperglycemia

Hyperglycemia is noted in more than half the patient's receiving PN [11, 12••]. The incidence and severity of PN associated hyperglycemia is higher compared to that seen with EN. In a meta-analysis of six randomized trials (264 critically ill patients with acute pancreatitis), the incidence of hyperglycemia was approximately two times greater for patients who received PN than for patients who received EN despite similar nutritional intake [19]. The reasons behind this difference are not well understood, although the incretin effect and elevation of endogenous insulin levels during EN may be contributing factors [20].

It is well established that the development of hyperglycemia during PN in the hospital setting is independently associated with higher rates of mortality and morbidity (Table 1). Mortality rates for patients with PN associated hyperglycemia are 2–11 times higher than for those without hyperglycemia, depending on the study setting and hyperglycemia definition. Lin et al. demonstrated that each 10 mg/dL increase in mean BG above a reference value of 114 mg/dL was associated with a 7–9% increase in the risk of infection and organ dysfunction [21]. Cheung et al. reported that mortality in patients with mean BG ≥164 mg/dL) was 11 times higher than that of patients with BG (124 mg/dL). It is noteworthy that this difference was more pronounced in individuals without diabetes mellitus [22] than those with diabetes. In the non-critical illness setting, a study of 605 patients showed that the patients who had mean BG >180 mg/dL during the PN infusion had a mortality risk that was 5.6 times greater than those with mean BG levels <140 mg/dL [25•]. This study demonstrated that the risk of having a capillary BG >180 mg/dL was greater in those patients who had high CRP levels, were >65 years old, had

Table 1 Adverse outcomes in patients with hyperglycemia receiving parenteral nutrition

	Cheung et al. [22]	Lin et al. [21]	Sarkisian et al. [24]	Pasquel et al. [23]	Olveira et al. [25•]
Blood glucose levels in mg/dL	<125 vs. >164	<114 vs. >180	>180	<120 vs. >180	<140 vs. >180
Mortality OR(95% CI)	10.9 (2.0–60.5)	5.0 (2.4–10.6)	7.22 (1.08–48.3)	2.8 (1.2–6.8)	5.6 (1.47–21.4)
Infectious complications OR(95% CI)	3.9 (1.2–12.0)	3.1 (1.5–6.5)	0.9[a] (0.3–2.5)	3.6[b] (1.6–8.4)	NR
Cardiac complications OR(95% CI)	6.2 (0.7–57.8)	1.6 (0.3–7.2)	1.3[a] (0.1–12.5)	NR	NR

NR not reported

[a] Non-significant

[b] Data reported for pneumonia only

HbA1c >5.7%, had diabetes, had infectious complications, or received more intravenous infusion of glucose [25•].

Farrokhi F et al. evaluated glycemic variability and clinical outcomes in 276 medical and surgical patients (19% with diabetes and 74% ICU setting) receiving PN. Glycemic variability was measured by the mean standard deviation (SD) of blood glucose values during PN and by the BG daily delta change (daily maximum minus the daily minimum blood glucose values). This study showed that high glycemic variability (SD: 48 ± 25 vs. 34 ± 18 mg/dL and Δ change: 75 ± 39 vs. 51 ± 29 mg/dL, both $P < 0.01$) is associated with increased hospital mortality independent of the presence and severity of hyperglycemia or hypoglycemia during PN therapy [26•].

It is important to recognize that, to date, there is insufficient randomized control trial (RCT) data to show that glycemic control reduces the risk of complications or mortality in patients receiving PN. However, given the increased risk of mortality and complications associated with hyperglycemia in patients receiving parenteral nutrition, it is important to recognize, prevent and treat hyperglycemia in these patients. Based on the evidence, American Society for Parenteral and Enteral Nutrition (ASPEN) recommends a BG target of 140–180 mg/dL in patients receiving nutrition support.

Prevention

The following approaches have been studied for prevention of hyperglycemia during PN.

- Decreasing dextrose content in PN
- Decreasing caloric content in PN
- Use of non-glucose carbohydrate in PN
- Combining EN and PN

The amount of dextrose, which is the major caloric source in PN, varies and is titrated according to individual factors such as severity of illness, caloric needs of the patient, and the patient's ability to tolerate fluid volume. Several studies demonstrated that PN dextrose content in excess of 4 mg/kg/min increases the risk of hyperglycemia in patients without diabetes. In a study done on 88 ICU patients without diabetes, parenteral nutrition with a dextrose infusion rate of 1.8 ± 1.3 g/kg/days was associated with less hyperglycemia, lower rate of insulin usage, and lower mortality rates compared with patients receiving PN with dextrose infusion rates of 2.6 ± 1.4 g/kg/days [27]. Hence, it may be reasonable to limit dextrose load in PN to 150–200 g/day as one of the measures to prevent the development of hyperglycemia during PN use [28].

Hypocaloric PN is associated with decreased hyperglycemia compared to standard calorie PN, 0% (95% CI, 0%–0.5%) vs. 33.1% (95% CI, 0%–58.4%; $P = 0.001$) [29]. Current nutritional guidelines recommend use of hypocaloric PN (≤20 kcal/kg/days or no more than 80% of estimated energy needs) with adequate protein (≥1.2 g protein/kg/days) over the first week of hospitalization as this reduces the potential for hyperglycemia and insulin resistance [30••].

In contrast to EN, there is limited data on use of non-glucose carbohydrates in PN. In a randomized controlled study of 138 patients with diabetes, use of glucose-fructose-xylitol in 2:1:1 ratio in PN did not have any advantage compared to glucose in PN in terms of hyperglycemia and insulin requirements [31].

In vitro studies showed that glutamine supplementation attenuates hyperglycemia and hyperinsulinemia [32]. Though glutamine supplementation has been shown to decrease hyperglycemia and insulin requirements [33], several recent trials and meta-analyses have brought into question the safety and efficacy of parenteral glutamine administration in critically ill patients. Data from a recent large RCT trial showed that mortality, in-hospital and at 6 months, was significantly higher in those patients who received glutamine compared with those who did not (37.2 vs. 31%; $P = 0.02$; 43.7 vs. 37.2%;) [34]. Current nutritional guidelines recommend that parenteral glutamine supplementation not be used routinely in the critical care setting [30••].

Another study showed that the combination of PN with EN (with EN providing 30% of the nutritional requirement) resulted in reduced glucose concentrations, reduced insulin

resistance, increased incretins and improvements in intestinal permeability [35].

To minimize the harmful effects of hyperglycemia seen with PN, it is important to assess nutritional status and clinical condition of the patient daily and as tolerance to EN improves, the amount of PN energy should be reduced and finally discontinued when the patient is receiving >60% of target energy requirements from EN [30••].

Treatment

If blood glucose values exceed 140 mg/dL despite active preventive measures described above then a therapeutic plan needs to be implemented. Insulin is the treatment of choice to control hyperglycemia during parenteral nutrition.

There are three general therapeutic strategies:

1. Using a separate infusion of regular insulin following an established IV insulin protocol. Advantages that this approach offers over use of subcutaneous insulin are achievement of tighter glycemic control. It allows for frequent dose adjustments and hence is more suitable for critically ill or hemodynamically compromised patients. Disadvantages include more nursing time required for patient care and risk of hypoglycemia if PN is discontinued without discontinuing the insulin infusion.

2. Using subcutaneous insulin in a regimen combining long or intermediate acting insulin with short- or rapid-acting correctional insulin. Advantages of this approach are less nursing time. Disadvantages include risk of hypoglycemia if PN is discontinued and long-/intermediate-acting insulin is still on board. This approach is also not suitable for cyclical PN. Neff et al. conducted a retrospective review to look at subcutaneous versus IV insulin in the management of hyperglycemia with PN. The IV group had significantly lower daily mean capillary BG (173 ± 38 mg/dL vs. 202 ± 47 mg/dL), and spent a greater proportion of time in the glycemic target range without any significant difference in hypoglycemia rates [36].

3. Adding regular insulin to PN bag and using subcutaneous short- or rapid-acting correctional insulin. Studies have shown that adding insulin to the PN bag is a safe and effective alternative [37–39]. The advantages of this method are less nursing time, insulin is concomitantly discontinued upon PN discontinuation, hence minimizing the risk for hypoglycemia. Disadvantages include the need to account for insulin binding to the infusion bag and tubing and the inability to immediately adjust insulin concentration in case of hypoglycemia. Different strategies were used to determine the dose of insulin to be added to the PN bag. The insulin dose was based on the previous 24-h intravenous insulin drip requirements [37] or subcutaneous sliding-scale requirements [38] or by use of insulin to dextrose ratios. There are only a few studies that have explored the efficacy of insulin to dextrose ratios.

In patients with diabetes, adding insulin at the ratio of 1 unit of insulin per 10 g of dextrose at the start of the PN infusion followed by daily titration of insulin by 0.5 unit per 10 g of dextrose if blood glucose target is not achieved has been found to be safe and effective [39].

In patients without diabetes, initiation of insulin at the rate of 1 unit per 20 g of dextrose followed by an upwards titration to a 1:15 ratio if blood glucose is above 140 mg/dL was reported to be effective by Jakoby et al. [40]. For patients with diabetes, the protocol used was significantly more complex as it combined use of NPH insulin to cover one third of insulin needs calculated according to a 1:10 dextrose ratio (the 2/3 of calculated ratio were added back to PN) with additional NPH given based on a weight-based calculation. While this combination was found to be safe and effective in managing hyperglycemia, due to its complexity a wide spread adoption of this approach may be difficult.

The GLUCOSE-in-PN study is the only randomized control trial that compared two different approaches. This prospective randomized control trial of 67 PN treatment episodes in non-critically ill patients with diabetes showed that both basal (glargine) insulin as subcutaneous injections and bolus (regular) insulin in the PN bag are effective modalities, there were no statistically significant differences in mean glucose values or overall glycemic control (52.24 vs. 47.76%) [41•].

Use of non-insulin agents in patients receiving PN has not been well studied. A pilot study by Nauck et al. evaluated nine surgical ICU patients (four with diabetes) on PN and eight healthy controls on intravenous glucose therapy. An infusion of biosynthetic GLP-1 significantly lowered glucose to normoglycemic levels in healthy controls and attenuated hyperglycemia in patients on PN from peak glucose of 211 to 159 mg/dL; seven out of nine patients had blood glucose less than 150 mg/dL on GLP-1 infusion [42]. Future trials are needed to further evaluate the efficacy of non-insulin therapies in treatment of hyperglycemia associated with PN.

Based on limited data, current recommendations for management of PN associated hyperglycemia are mostly based on expert opinion as summarized in Table 2.

Authors Recommendations

For patients without diabetes who develop persistent hyperglycemia with BG >140 mg/dL while on PN and need correctional insulin for 12–24 h, a combination of regular insulin in the PN bag and subcutaneous short/rapid-acting correctional insulin every 4–6 h can be used. Initial insulin to dextrose ratio

Table 2 Recommendations from various societies for management of TPN associated hyperglycemia

Society	Recommendations
ADA Standard of Medical Care in Diabetes 2017 [1••]	For patients with diabetes—add regular insulin to PN bag, start with 1 unit per 10 g of carbohydrate and adjust daily. Supplement with correctional subcutaneous insulin every 4–6 h
Endocrine Society 2012 [43]	Regular insulin as part of PN and subcutaneous correctional insulin. Separate insulin infusion can be used for dose finding.
Society of Hospital Medicine 2016 glycemic control implementation guide [44]	[a]Initially a separate insulin infusion for accurate dose finding. Then regular insulin can be added to subsequent PN bags, supplement with subcutaneous correctional insulin.

[a] Preferred regimen

of 1:20 may be used with up-titration to 1:15 if blood glucose is above target.

For patients with diabetes, a combination of regular insulin in the PN bag, basal insulin and subcutaneous short-/rapid-acting correctional insulin every 4–6 h may be used. Insulin to dextrose ratio of 1:15–1:10 can be used initially with up-titration as needed. The pre-admission basal insulin dose can be continued, but caution should be taken if there is any associated renal dysfunction. Alternatively, a weight-based dose of 0.1–0.2 units/kg/day of long-acting insulin (detemir or glargine) can be used as basal insulin. There is very limited data on the use of longer-acting basal insulin (U100 & U200 degludec, U300 glargine, U-500 human insulin) in the inpatient setting, hence we do not recommend using these insulins.

Caution should be used in patients who are hemodynamically unstable with variable doses of pressors, steroids or renal dysfunction. Those patients are safer if managed with separate insulin infusion until a relative stability has been reached. At that point, 80% of the insulin total daily dose can be added as regular insulin to the subsequent PN bags, supplementing with subcutaneous correctional insulin if needed.

Enteral Nutrition

Enteral nutrition is commonly used in hospitalized patients who are unable to meet their nutritional goals via oral intake. Short-term EN support (<4 weeks) is often propagated through the use of nasogastric or nasoenteric tubes. Less frequent in practice, the need for long-term (>4 weeks) EN support can be accomplished through percutaneous gastro/jejunal placement.

Evidence supporting the use of EN in the delivery of specialized nutrition includes the beneficial effects this form of nutrition support has on maintaining GI and immunological physiology. EN has been shown to diminish systemic inflammation in the presence of malnutrition and has been shown to negate the risk of line infections well-documented to accompany the use of PN [43].

The most common modes of delivery for tube feedings include the use of continuous, bolus or nocturnal infusions. Lasting an entire day in duration, continuous EN delivers a constant source of nutrition to the patient. Bolus tube feeds are the most physiologic in terms of delivering EN in the form of multiple meals throughout the day, mimicking what one would receive from an oral diet. Lastly, nocturnal tube feed administration usually starts late in the evening and supplies EN over the course of 8 to 12 h overnight.

Much advancement in the creation of disease specific EN formulas has occurred within the past two decades, providing clinicians with an even greater selection of nutritional supplementation.

Enteral Nutrition and Hyperglycemia

Roughly 30% of hospitalized adult patients and up to one-half of elderly patients within long-term care facilities that receive EN will experience hyperglycemia [45, 46]. This metabolic adverse event is not limited solely to diabetes patients. Hyperglycemia in patients receiving EN without diabetes results in an increased risk of mortality in relation to their diabetes comparators [47, 48].

The exact mechanism by which hyperglycemia occurs in patients receiving EN is unknown. It is theorized to result by way of continual exposure of glucose within the intestinal tract thus impacting the secretion and action of incretin hormones (glucagon-like peptide-1 [GLP-1 RA] and gastric inhibitory polypeptide [GIP]) [49–51]. Other contributing factors include increased hepatic glucose production, as well as reduced peripheral utilization caused by stress and increased levels of cytokines and stress hormones such as glucagon, cortisol, and catecholamine [52].

Individuals that go on to experience hyperglycemia while receiving EN are at great risk for the development of metabolic derangements. Examples of such metabolic derangements known to be deleterious to the health of patients includes the formation of oxidative stress, emergence of inflammation and

tissue damage at the systemic level, as well as an increase in insulin resistance [53–56].

Prevention of Hyperglycemia

Tube Feed Formulas

Tube feeding formulas may be grouped into standard, elemental (semi-elemental), and disease specific formulas. In terms of carbohydrate content, various formulations contain anywhere from 112 (Replete Fiber) to 204 g (VIVONEX T.E.N.) of carbohydrate per liter. Given the known influence of carbohydrate content on blood glucose [57], diabetes specific formulas (DSFs) were developed with the aim to limit the occurrence of glycemic variance in patients receiving EN. Specifically, DSFs diverge from standard EN formulations with the use of monounsaturated fatty acids (MUFAs), increased amount of fiber and lower total carbohydrate content, ranging from 100 (Nutren Glytrol) to 132 g (Glucerna 1.5) of carbohydrate per liter. For example, Glucerna 1.5 is comprised of complex carbohydrates that protract digestion and absorption of the infused carbohydrate; aimed at blunting the rise in postprandial glucose levels [57, 58].

Assertions pertaining to improved glycemic outcomes in patients with diabetes utilizing DSFs have been replicated in several studies as well as in meta-analyses [59–68]. While glycemic measurements (e.g., glycemic index, A1c, etc.) have been noted to improve with DSF use, robust data to support the improvement in morbidity and mortality is lacking. Recently, evidence from three trials has furthered the body of literature supporting the use of DSFs for glycemic improvement. Mesejo et al. and Sanz-Paris et al. demonstrated that use of DSFs in an ICU and outpatient setting improved glycemic outcomes while minimizing complications during hospitalization and overall healthcare utilization among outpatients [69•, 70]. Han et al. provided evidence from a retrospective analysis that demonstrated improvement in mortality in an ICU setting in type 2 diabetes (T2DM) patients receiving DSF [71].

Given the limited evidence supporting the use of DSFs with the goal of mitigating clinical outcomes other than that of hyperglycemia, ASPEN does not recommend the use of DSF in patients receiving EN as an effective means to manage hyperglycemia [72]. Due to the potential to lower glycemic index, use of DSFs in conjunction with other glycemic control strategies may be worthwhile. Given the consistency in improvement of glycemic outcomes, the European Society of Clinical Nutrition and Metabolism (ESPEN) expert group endorses the use of DSF in patients with a history of diabetes or obesity [73•].

Tube Feeding: Target Blood Glucose

A concerted effort should be made to attain a glycemic goal of 140–180 mg/dL in hospitalized adult patients receiving special nutrition by way of EN, a range recommended by ASPEN [72]. Justification for this range, stems from several large clinical trials published within the past decade demonstrating that attainment of glycemic goals lower than 140 mg/dL does not delineate improvement in clinical outcomes [74–79].

Tube Feeding: Blood Glucose Monitoring

Clinicians should monitor blood glucose levels in all patients upon initiation of EN, with or without diabetes, every 4 to 6 h, or as deemed appropriate secondary to the form of delivery of the EN. Blood glucose monitoring may be discontinued in patients without a past medical history of diabetes in the absence of BG elevation (>140 mg/dL) in 24 to 48 h [43].

Pharmacological Mitigation Strategies in the Management of Hyperglycemia Associated with EN

Insulin

Scheduled insulin therapy is indicated in the treatment of patients with or without diabetes receiving EN at blood glucose levels greater than 140 mg/dL in the presence of persistent requirements of correction scale insulin (i.e., 12–24 h) (43). When selecting an insulin regimen for a patient, clinicians should match the specific pharmacokinetics/pharmacodynamics of a given insulin preparation to the EN schedule of delivery (i.e., continuous, bolus, cyclic, etc.).

Patients receiving continuous tube feeds are essentially in a constant postprandial state. Thus, delivery of a continuous infusion of intravenous regular insulin is well regarded as a safe and effect delivery mechanism of administering insulin to patients receiving EN, especially those patients receiving care in an ICU setting [80]. However, given the amount of resources required (staffing, more frequent glucose monitoring, etc.) to safely and effectively deliver a continuous insulin infusion, alternative delivery strategies in the form of subcutaneous insulin are often warranted, especially in the non-critical care setting.

Currently, various subcutaneous insulin treatment approaches exist in the selection of an insulin regimen to match EN delivery. Evidence supporting the use of subcutaneous insulin in the management of patients receiving continuous EN can be extrapolated from three clinical trials.

Korytkowki et al. published the first and only RCT evaluating glycemic outcomes in non-critically ill patients receiving continuous EN [80]. Fifty patients were randomized to receive either empiric (10 units per day) or an equivalent previously required dose of insulin glargine plus regular insulin

Table 3 Recommendations from various societies for management of continuous enteral nutrition associated hyperglycemia

Society	Insulin recommendations		
	Basal	Nutritional	Correction insulin
American Diabetes Association (2017) [1••]	• Continue prior basal dose • If none: Calculate TDD[a] of insulin OR Empiric NPH/detemir 5 units SubQ every 12 h Empiric Glargine 10 units SubQ daily	• Rapid-acting insulin every 4 h (start with 1 unit for every 10–15 g of carbohydrate, adjust daily) OR • Regular insulin every 6 h (start with 1 unit for every 10–15 g of carbohydrate, adjust daily)	• Regular insulin every 6 h OR • Rapid-acting insulin every 4 h
Endocrine Society (2012) [43]	• Administer once (glargine/detemir) OR twice daily (detemir/NPH)	• Rapid-acting insulin every 4 h OR • Short-acting insulin every 6 h	
Society of Hospital Medicine (2016) [44]	• Accounts for 40–50% of TDD[a] of insulin Glargine SubQ daily OR Detemir SubQ twice daily	• Accounts for 50–60% of TDD[a] of insulin (in divided doses) Rapid-acting insulin every 4 h Short-acting insulin every 6 h	• Match with nutritional insulin choice

TDD of insulin may be estimated by utilizing the following weight-based estimates: 0.2–0.3 units per kg per day = ≥70 years of age, very lean, very sensitive to insulin, new hyperglycemia; 0.4 units/kg per day = normal body habitus and history of diabetes; 0.5 units/kg per day = overweight and history of diabetes; 0.6–0.8 units/kg per day = obese, on corticosteroids, or known to be insulin-resistant

SubQ subcutaneous, *Rapid-acting insulin* aspart, glulisine, lispro

[a] *TDD* total daily dose

Table 4 Recommendations from various societies for management of bolus enteral nutrition associated hyperglycemia

Society	Insulin recommendations		
	Basal	Nutritional	Correction insulin
American Diabetes Association (2017) [1••]	• Continue prior basal dose • If none: Calculate from TDD[a] OR NPH/determir 5 units SubQ every 12 h Glargine 10 units SubQ daily	• Administer rapid-acting insulin OR regular insulin before each feeding (start with 1 unit for every 10–15 g of carbohydrate, adjust daily)	• Regular insulin every 6 h for hyperglycemia OR • Rapid-acting insulin every 4 h for hyperglycemia
Endocrine Society (2012) [43] *Society of Hospital Medicine (2016)* [44]	• Accounts for 50% of TDD[a] of insulin Glargine SubQ daily OR Detemir SubQ twice daily	• Administer rapid-acting or short-acting insulin before each bolus administration of EN Accounts for 50% of TDD[a] of insulin Rapid-acting insulin for each bolus	Rapid-acting insulin for each bolus

TDD of insulin may be estimated by utilizing the following weight-based estimates: 0.2–0.3 units per kg per day = ≥70 years of age, very lean, very sensitive to insulin, new hyperglycemia; 0.4 units/kg per day = normal body habitus and history of diabetes; 0.5 units/kg per day = overweight and history of diabetes; 0.6–0.8 units/kg per day = obese, on corticosteroids, or known to be insulin-resistant

SubQ subcutaneous, *Rapid-acting insulin* aspart, glulisine, lispro

[a] *TDD* total daily dose

correction scale ($n = 25$) every 4 to 6 h versus regular insulin sliding scale (RISS) alone ($n = 25$) administered every 4 to 6 h. Use of twice daily NPH insulin was added to subjects receiving RISS alone in the presence of two or more blood glucose readings found to be greater than 180 mg/dL. No statistical differences were found to exist among subject groups in regards to glycemic control, hospital length of stay, or total adverse event occurrences. However, 48% of participants assigned to RISS alone required the use of NPH insulin in the management of persistent hyperglycemia. Cook et al. conducted a retrospective review evaluating glycemic outcomes in patients who were administered three differing treatment strategies including sliding-scale NPH insulin administered every 4 h and sliding-scale NPH insulin administered every 6 h to patients who had received sliding scale, insulin aspart alone (all sliding scale insulin was based on current BG) [81]. Patients receiving either form of sliding-scale NPH treatment (every 4 h or every 6 h) attained statistically lower mean blood glucose values compared to patients who had received sliding-scale insulin aspart alone ($P < 0.001$). A statistically significant difference in hypoglycemia occurrence was observed in patients receiving sliding-scale insulin NPH every 4 h over that of sliding-scale insulin aspart ($P = 0.03$). Last, Hsia et al. compared the effectiveness of biphasic insulin 70/30 to that of a basal/bolus (glargine/lispro) regimen in managing hyperglycemia in 22 non-critically ill diabetes patients receiving continuous EN [82]. Subjects that received 70/30 biphasic insulin TID, were found to consistently be within the defined glycemic goal of 140–180 mg/dL (69% of values) versus patients that had received 70/30 biphasic insulin BID regimen (22% of values) or those that received a glargine/lispro regimen (24% of values). Finally, the frequency of hypoglycemia (defined as <70 mg/dL) was found to occur less often in subjects who had received the 70/30 biphasic insulin TID regimen (1.4%) compared to participants that had received 70/30 biphasic insulin BID (2.1%) or the glargine/lispro regimen (5.4%). When using pre-mix insulin in the hospital setting in addition to basal and bolus insulin, staff education is key to prevent "look alike-sound alike" insulin errors.

Currently, no evidence exists comparing insulin utilization in the management of hyperglycemia in patients receiving bolus or nocturnal tube feeds. Based upon available published data, Tables 3 and 4 list insulin recommendations from three major organizations (American Diabetes Association, Endocrine Society, and Society of Hospital Medicine) in the delivery of EN via continuous or bolus tube feeds [1••, 43, 44]. Author recommendations for physiological approaches to subcutaneous insulin administration for continuous, bolus and nocturnal EN administration are outlined below:

Continuous Tube Feeds

1. NPH insulin administered every 8 h (40–50% of TDD) in addition to rapid-/short-acting nutritional insulin (50–

60% of TDD) plus rapid-/short-acting correction scale insulin administered every 4 to 6 h.
2. Biphasic 70/30 insulin administered every 8 h in addition to short-acting correction scale insulin administered every 8 h.
3. Basal insulin administered daily (glargine) or every 12-h (detemir) (40–50% of TDD) in addition to rapid-/short-acting nutritional insulin (~60% of TDD) plus rapid-/short-acting correction scale insulin administered every 4 to 6 h.

Bolus Tube Feeds

1. Basal insulin administered daily (glargine) or every 12 h (detemir) (according to weight-based calculation) in addition to scheduled rapid-acting insulin (according to insulin to carbohydrate ratio) plus correction scale insulin administered with bolus EN administration.

Nocturnal Tube Feeds

1. NPH or biphasic 70/30 insulin administered at commencement. Correction rapid/short-acting can be administered accordingly to optimize control.

Non-insulin Treatment Modalities

There has been a growing interest in the use of non-insulin injectables and oral anti-hyperglycemic treatment modalities in the management of hyperglycemia among hospitalized patients [83•]. Given the absence of primary literature supporting the use of these agents in patients receiving EN, as well as the known limitations associated with given classes of anti-hyperglycemic agents when used in hospitalized patients, the authors cannot recommend their use. Future investigation and research demonstrating the utility of these agents in providing safe and effective control of blood glucose in patients receiving EN is needed.

Summary and Conclusion

There is an under appreciation of the contribution of nutritional intake, or lack thereof, to glycemic management in the hospital setting. In this overview, we have provided an approach to the management of patients on meals on demand, EN or PN, highlighting the challenges of matching insulin dosing to the actual number of carbohydrates consumed. There is very little published data that guides the management of these patients. This means that many of the recommendations reflect consensus opinion that incorporates knowledge of the pharmacokinetics of different insulin and oral preparations, glucose metabolism, published literature, as well as extensive clinical experience.

Compliance with Ethical Standards

Conflict of Interest Andjela T. Drincic has received consultant honorarium from Bayer.

Jon T. Knezevich and Padmaja Akkireddy declare that they have no conflict of interest.

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

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