

Inpatient and perioperative management of hyperglycemia

Department of Internal Medicine Grand Rounds
July 7, 2017

Luigi Meneghini discloses that he has served on advisory boards and as consultant for both Sanofi Aventis and Novo Nordisk. He will not be discussing off label uses of any product during his presentation.

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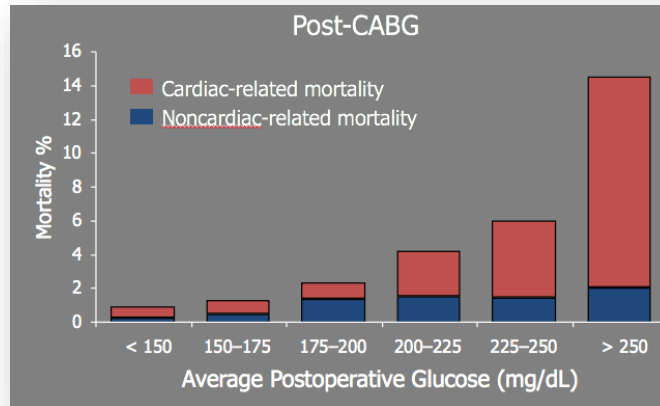
Dr. Meneghini joined UT Southwestern in January of 2014 after a 20-year tenure at the University of Miami Miller School of Medicine. His primary interests lie in improving the lives of patients with diabetes through the application of cutting edge therapies and technologies, the practical implementation of effective treatment strategies at both the individual and system level, and education of patients and professionals. He has been involved in the development of treatment algorithms for glycemic control of insulin treated diabetes. At Parkland, he is charged with implementing a system-wide program to organize, integrate and optimize diabetes management among primary, specialty and acute care settings, leveraging IT and population health expertise, community resources and human capital to reduce chronic disease burden. Dr. Meneghini is a frequent lecturer, well published and internationally recognized. Born in Italy, raised in Liberia and naturalized in the US, he speaks Italian, French, English, and Spanish fluently.

The purpose of this presentation is to update the audience to the latest evidence supporting tools and targets to optimize the management of hyperglycemia for hospitalized or perioperative patients. We will discuss the current guidelines for establishing glycemic targets in the acute care setting, along with some of their historical context. A discussion of physiologic insulin replacement, anchored on the concepts of basal, nutritional and corrective insulin replacement will be followed by interactive case presentations to underscore various common, and often tricky to manage, scenarios such as how to handle NPO patients, patients on enteral feeds and patients with corticosteroid-exacerbated hyperglycemia. We will begin our discussion of perioperative diabetes management by reviewing the evidence linking hyperglycemia to poor outcomes and examine glycemic targets both in preparation for elective surgery and for the perioperative period. Additionally, we will discuss perioperative management strategies, including what to advise patients coming in for surgery, appropriate insulin management strategies and some of the ongoing efforts to optimize glycemia at Parkland Hospital.

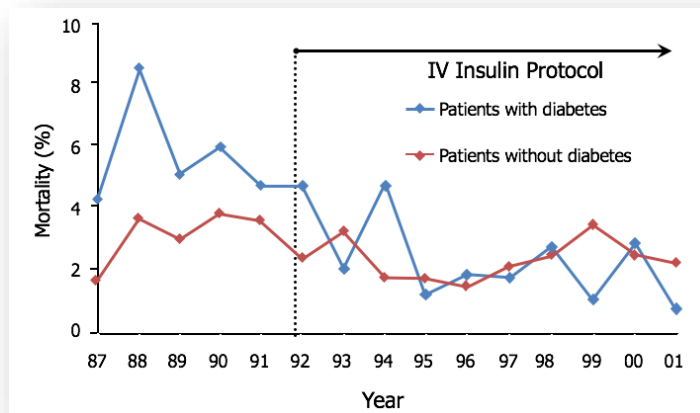
At the conclusion of this lecture, the listener should be able to:

- Determine inpatient and perioperative glycemic targets for patients with diabetes and hyperglycemia
- Formulate a basal/bolus insulin prescription to manage patients with hyperglycemia admitted to the hospital
- Demonstrate how to match insulin replacement to enteral nutritional supplementation to control hyperglycemia
- Manage glycemic therapies in patient with diabetes going to surgery

Inpatient management of hyperglycemia has evolved over the past few decades, and with growing evidence base and better technologies, will continue to do so in the foreseeable future. A number of studies over the years have highlighted the relevance of glycemic control in the hospital and perioperative setting. Furnary and his group, among others, clearly established the relationship between elevated blood glucose levels and post-operative morbidity and mortality in their reports of patients undergoing cardiothoracic surgery¹.



Importantly, they demonstrated a remarkable reduction in post-operative mortality in patients with diabetes undergoing coronary artery bypass grafting, following the implementation of IV insulin protocols. Others have also shown the relationship between elevated blood glucose levels and morbidity following non-cardiac surgery².



In her seminal publication in 2001, Van Den Berghe demonstrated that it was possible to tightly control blood glucose levels in critically ill patients, aiming for a target range between 80-110 mg/dl, which compared to conventional treatment resulted in a reduction in morbidity and

mortality in those patients³. The enthusiasm for aggressive insulin management in critical care units was considerably dampened with the publication of the NICE-SUGAR study in 2009, which clearly linked the increased severe hypoglycemia rate seen in the tightly controlled patient arm with a clinically and statistically increased risk of death⁴. The authors concluded that a blood glucose target of ≤ 180 mg/dl resulted in “lower mortality than did a target of 81-108 mg/dl”. Based on the available evidence, and recognizing the limitations of current tools and technologies in attempting to normalize glycemic levels in critically ill patients, the professional organizations have since modified their recommendations for appropriate glycemic targets in the ICU setting⁵. Currently, it is understood that in the ICU IV insulin treatment needs to be considered when blood glucose levels exceed 180 mg/dl, with an initial glycemic target range between 140-180 mg/dl. If blood glucose levels are stable and in selected patients, expanding the target range to 110-180 mg/dl may be appropriate. Blood glucose levels below 110 mg/dl are not recommended and should be avoided in order to minimize the risk of hypoglycemia in general, and severe hypoglycemia in particular.

AACE/ADA Recommended Target Glucose Levels in ICU Patients

ICU setting:

- Starting threshold of no higher than 180 mg/dL
- Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL
- Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients

Not recommended <110	Acceptable 110-140	Recommended 140-180	Not recommended >180
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The evidence supporting glycemic target recommendations for non-critical care settings is less robust; nevertheless, the recommendations for management of hyperglycemia on the ward calls for pre-meal or fasting blood glucose targets of < 140 mg/dl and random blood glucose levels < 180 mg/dl⁶. In addition, they recommend reassessing the insulin regimen if blood glucose levels fall below 100 mg/dl, but recognize that some patients may be maintained with a glucose range below and/or above these cut-points.

The definition used for hypoglycemia in the inpatient setting differs from that traditionally used for outpatient care, recognizing that hospitalized patients may not always be in the condition to recognize hypoglycemia or alert the appropriate care provider. In the hospital setting, hypoglycemia is defined as any value under 70 mg/dl, which severe hypoglycemia is a blood glucose < 40 mg/dl⁵.

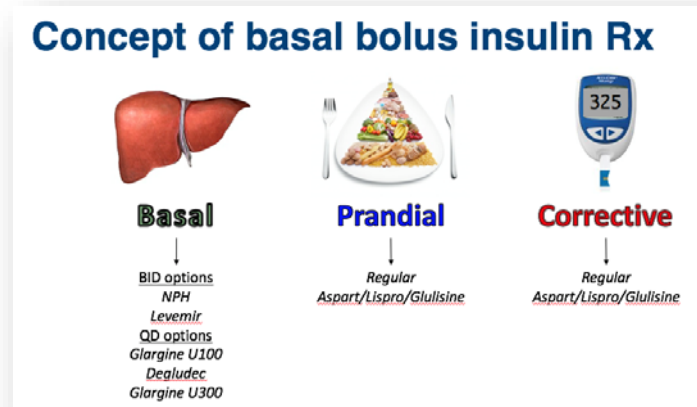
Patients admitted to the hospital with a diagnosis of diabetes, or found to have hyperglycemia on admission, should have an A1C (HbA1c, glycated hemoglobin) test completed to assess the

degree of glycemic exposure for the preceding 2-3 months. In patients with blood loss or transfusion, on dialysis or high dose salicylates, or with hemoglobinopathies, all of which might interfere with the accuracy of HbA1c, a fructosamine level can be ordered. The results can be helpful in determining what approach to take for glycemic management during the hospitalization, and importantly can assist in determining the appropriate glycemic management plan to recommend on discharge from the hospital. All patients, regardless of diagnosis, should have a laboratory plasma glucose performed on admission, and those without a history of diabetes, but with a blood glucose > 140 mg/dl should be monitored with point-of-care (POC) blood glucose testing. Of note, is that around a third of patients presenting with hyperglycemia on admission do not carry a prior diagnosis of diabetes; these patients actually have a higher mortality risk during the hospitalization than those with a diagnosis of diabetes⁷.

Currently, the majority of patients admitted to the hospital should have their oral antidiabetic agents discontinued, including injectables such as GLP-1 receptor agonists (exenatide, liraglutide, dulaglutide, etc.)⁶. Sulfonylureas and glinides increase the risk of hypoglycemia overnight and when the patient is fasting, while metformin is contraindicated in patients with advanced renal dysfunction, hemodynamic instability or requiring IV contrast agents for radiologic procedures. SGLT-2 inhibitors can be associated with volume depletion and electrolyte abnormalities and GLP-1 receptor agonists might exacerbate gastrointestinal symptomatology. Thiazolidinediones should be stopped in case of fluid retention, congestive heart failure or pulmonary edema. DPP-4 inhibitors are the one class of drugs that may be continued on admission, since on their own they do not cause hypoglycemia and have a low side effect profile; in fact, this class of medication is currently being tested in hospitalized patients as a complement to insulin therapy⁸. If glycemic management is needed during hospitalization, subcutaneous insulin therapy consisting of basal insulin replacement (long-acting analog given QD or intermediate-acting NPH administered twice daily), along with rapid or short-acting insulin for correction of hyperglycemia and coverage of nutritional intake, is recommended⁶. Pre-mixed insulin formulations (70/30, 75/25) are seldom appropriate for inpatient use, except in certain rare circumstances, such as coverage of tube feeds. In ICU settings, IV insulin infusions are preferred for managing hyperglycemia due to their more rapid onset of action and more flexible dosing options, which are often needed in critically ill patients whose blood glucose are affected by stress of illness, medications (e.g. steroids, catecholamines), nutrition replacement (enteral or parenteral) and hemodynamic instability.

Physiologic insulin replacement consists of providing insulin to cover basal insulin needs (usually associated with endogenous, hepatic glucose production) and nutritional insulin needs (associated with administration of exogenous carbohydrates via meals or enteral/parenteral formulations). In addition, people with diabetes will experience hyperglycemia, which needs to be corrected with additional (supplemental) doses of insulin. Basal insulin options include intermediate-acting NPH insulin (dosed twice daily), long-acting insulin analogs, such as glargine U-100 and detemir insulin (dosed once or twice daily), and the newest ultra-long acting basal analogs, degludec and glargine U300 (dosed once daily). Basal insulin replacement is meant to maintain stable blood glucose levels while the patient is not eating (such as in-between meals and overnight), and therefore if indicated, should not be withheld in patients that are placed NPO (nil per os or nothing by mouth). If anything, the basal insulin dose might need to be

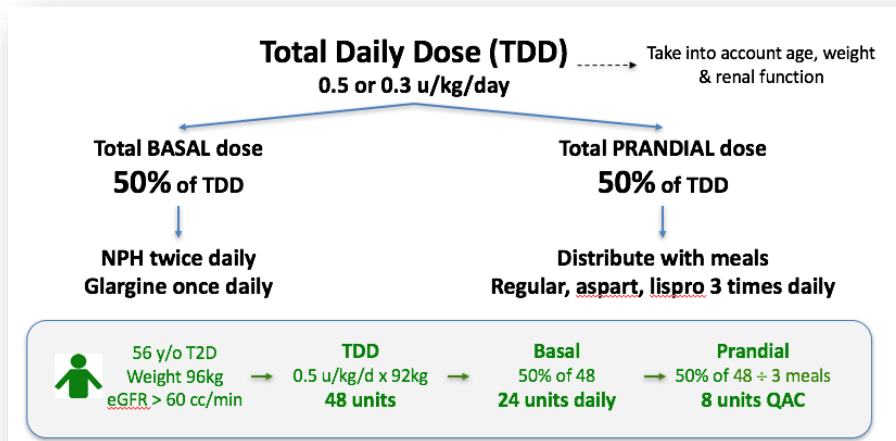
slightly decreased pre-operatively depending on whether the administration occurs the evening before or the morning of surgery (more to come later in the text). For prandial/mealtime or corrective insulin replacement, short-acting insulin (Regular), or rapid-acting analogs (Aspart, Lispro, Glulisine) are used; nutritional coverage of enteral feeds can be done with either a short or rapid-acting insulin, or an intermediate acting NPH preparation. We prefer to keep the nutritional and basal preparations separate when covering enteral feeds.



The initial prescription for patients admitted to the hospital requires the estimation of a Total Daily Dose (TDD) of insulin. This represents our best estimate of what the patients basal and prandial insulin requirements might be over the course of a 24-hour period. The TDD can be estimated with a weight-based calculation, or taking into account a patient's outpatient insulin prescription. For example, a patient on premix 70/30 injecting 25 units twice a day, would have a TDD of 50 units. The latter can be considered as long as the provider is confident that the patient has been adherent to their insulin schedule and that their caloric intake (specifically their carbohydrate intake) will be similar in the hospital as it is at home. Even when these circumstances are met, a 20% reduction in insulin dose might be prudent.

The weight based calculation can be used for patients who are insulin naïve, on an insulin schedule that is probably not appropriate for the hospital setting, or in whom questions of adherence loom. In this case, the patient's actual weight in kilograms can be multiplied by a factor to determine the TDD. An appropriate factor for most patients with diabetes (type 1 and not severely resistant type 2) is 0.5 units/kg/day. This factor can be decreased to 0.3 units/kg/day in older patients (e.g. > 70 years) or those with a low eGFR (e.g. < 45 ml/min/1.73 m²). For example, the TDD for a 96-kg patient would be 48 units, unless they were older or with renal insufficiency, in which case they would start with 29 units.

Once the TDD is estimated, then 50% of the amount is used for basal insulin replacement and the other 50% distributed among the three scheduled daily meals. For example, in our 96-kg patient basal insulin replacement would be accomplished with either NPH 12 units BID or glargine U-100 24 units daily. Mealtime or prandial coverage could be achieved by using Regular insulin or one of the rapid-acting analogs and administering 8 units with meals.



Finally, a correctional scale can be selected and adjusted by using a patient's TDD as a surrogate for insulin sensitivity. Patients starting on less than 40 units TDD a day could use a low correction scale, those needing 40-80 units a day with a moderate correction scale, and those requiring >80 units daily on a high correction scale.

Correction Scales Based on TDD

Low Dose: TDD < 40 units/day		Medium Dose: TDD 40-80 units/day	
Pre-meal BG (mg/dl)	Additional insulin	Pre-meal BG (mg/dl)	Additional insulin
150-199	1 unit	150-199	1 unit
200-249	2 units	200-249	3 units
250-299	3 units	250-299	5 units
300-349	4 units	300-349	7 units
>349	5 units	>349	8 units

High Dose: TDD > 80 units/day		Individualized Algorithm	
Pre-meal BG (mg/dl)	Additional insulin	Pre-meal BG (mg/dl)	Additional insulin
150-199	2 units	150-199	___ unit(s)
200-249	4 units	200-249	___ units
250-299	7 units	250-299	___ units
300-349	10 units	300-349	___ units
>349	12 units	>349	___ units

While analog insulin preparations are more physiologic than human insulin (Regular and NPH), in the inpatient there are no studies that show better glycemic control using these more expensive analogs^{9,10}. Insulin doses can then be adjusted over the course of the hospitalization based on inpatient conditions and variables, as well as the patient's glycemic response. The fasting blood glucose is usually useful to gauge basal insulin replacement, while the pre-lunch,

pre-dinner and bedtime glucose levels provide information on the prandial coverage at breakfast, lunch and dinner, respectively.

During hospitalization, nutritional coverage may need to take the form of carbohydrate coverage from enteral or parenteral delivery of nutrients. While in these patients the concepts of basal insulin replacement and amounts discussed previously still stand, the approach to covering these types of carbohydrates needs to be more targeted. Specifically, we would recommend estimating the carbohydrate content administered over a specific period of time and use an insulin-to-carbohydrate ratio (ICR) to match short- or rapid-acting insulin to nutrient delivery. Start with 1 unit of insulin to cover 10-15 grams of carbohydrates, and then adjust the ratio based on the patient's glycemic response. For enteral feeds, Regular insulin every 6 hours or one of the rapid-acting analogs every 4 hours can be used to match nutrient delivery. While NPH and occasionally glargine insulin can be used, split into 1-2 daily doses, to match carbohydrate intake, their use for nutritional coverage may be confused with basal insulin needs; we prefer to reserve their use for overnight coverage of enteral feeds, if at all, to minimize sleep disruption.

Enteral (tube) feeds

- **Enteral feeds: continuous**

- Use Regular insulin (Q6 hrs) or rapid-acting insulin analog (Q 4hrs)
- Start 1 unit of insulin SQ to cover 10-15 grams of carbohydrates

- **Enteral feeds: bolus**

- Start 1 unit of insulin SQ per 10-15 grams of carbohydrates (inject 15-20 min prior to bolus)

- **Enteral feeds: nocturnal**

- Consider NPH insulin SQ 1 u per 10-15 gram of carbohydrates

Parenteral insulin coverage can be calculated in a similar manner by using 1 unit of Regular insulin for every 10-15 grams of dextrose estimating contained within a bag of parenteral solution. The daily order for Regular insulin to be placed in the total parenteral nutrition (TPN) bag can then be adjusted based on the patient's glycemic excursions while on hyperalimentation.

Another common variable encountered in the hospital setting is the use of corticosteroids in pharmacologic doses to manage conditions that vary from inflammation, to tissue rejection to adrenal replacement. Corticosteroids can exacerbate hyperglycemia through an increase in insulin resistance that usually is most manifest 4-6 hours after administration, and can last more than 16 hours^{11,12}. Patients on corticosteroids should be monitored for at least 24-48 hours during hospitalization and be provided with a correction scale in the case of hyperglycemia. Persistent hyperglycemia due to steroids should be managed with additional insulin coverage¹³. This can take the form of an increase in prandial insulin doses during the

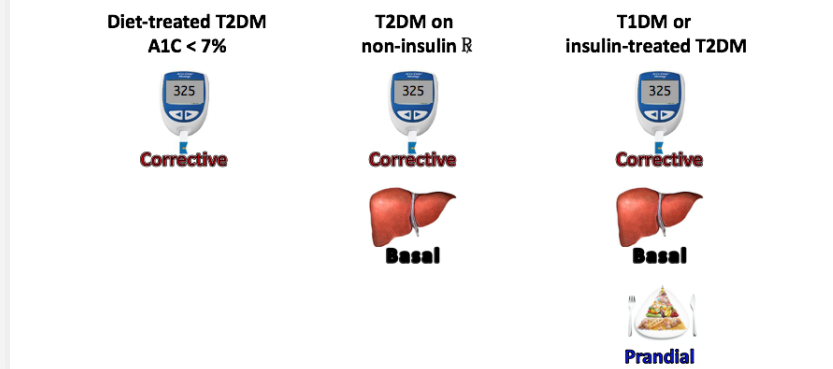
period of insulin administration, and possibly an adjustment in the correctional insulin scale. Another option that has been proposed is to match morning corticosteroid administration to a dose of NPH insulin, concomitantly administered. Briefly, a 10mg dose of prednisone (or another equivalent corticosteroid amount) would be matched with a 0.1 units/kg dose of NPH, and the dose of NPH increased by 0.1 units/kg for every 10 mg increase in prednisone dose equivalent, up to a maximum of 0.4 units/kg¹⁴. For example, a 100kg person experiencing hyperglycemia due to 20 mg of prednisone could be given a 20-unit dose of NPH insulin (100kg times 0.2 units/kg) at the time of steroid administration.

Suggested Dosages of NPH Insulin for Tapering Dosages of Glucocorticoids	
Prednisone dosage (mg/d)	Insulin dosage (U/kg)
≥40	0.4
30	0.3
20	0.2
10	0.1

Patients with hyperglycemia admitted for surgery can be managed with insulin using many of the same concepts discussed in physiologic insulin replacement. With basal, prandial and corrective insulin replacement, the one constant is that prandial insulin is suspended when the patient is placed NPO. All patients should be monitored with POC glucose testing and all patients prescribed a correction scale to correct hyperglycemia. For perioperative patients, the recommendations for blood glucose targets vary slightly among professional groups^{15,16}; a range between 100-220 mg/dl is generally appropriate for most. At Parkland, we aim to keep glucose values between 110-180 mg/dl (in line with the wider critical care setting range) and start correctional insulin when blood glucose exceeds 180 mg/dl.

As a guideline, patients with diet-treated type 2 diabetes and acceptable glycemic control (A1C < 8%) can be initially placed on a correctional scale only, and basal insulin added in case they experience persistent hyperglycemia. Those with type 2 diabetes treated as outpatients on non-insulin anti-glycemics should probably be started on basal insulin replacement, as described earlier, along with correctional insulin for managing hyperglycemia. Patients with insulin treated type 2 diabetes will probably do best on full physiologic replacement with basal, correctional and while they are still eating, prandial, insulin coverage. Basal insulin should never be held or stopped in individuals with type 1 diabetes, regardless of PO status; the only exception might be in those placed on IV insulin infusions.

Pre-operative insulin management in the admitted patient



Debate continues regarding the level of acceptable glycemic control in patients undergoing elective procedures¹⁷⁻¹⁹. While prospective data to address the issue is for the most part lacking, the American Diabetes Association, the National Health Service in the UK and the American College of Surgeons endorse an A1C < 8.5% as an acceptable pre-operative level of control. Pre-operative instructions that should be applied to patients undergoing elective surgery include the suspension of all oral anti-diabetic agents and non-insulin injectables on the morning of surgery, as well as skipping the prandial insulin dose if the patient is NPO. For individuals on basal insulin replacement at home the suggestions are as follows^{15,16}. For NPH insulin, reduce the dose by 20% the evening prior to surgery and by 50% the morning of surgery. For long-acting basal insulin analogs consider reducing the dose by 20%, especially if they are administered in the morning. For patients on premixed insulin preparations, they should take their usual dose the evening before surgery (before dinner) and reduce the dose by 50% the morning of surgery. In patients with a history of hypoglycemia in the morning, or with blood glucose levels consistently under 100 mg/dl, additional reduction in the dose might be warranted.

Basal insulin adjustments pre-operatively

	Night/evening before surgery	Morning/day of surgery
Intermediate-acting (NPH)	↓ 20%	↓ 50%
Long-acting (Glargine, Detemir, Degludec)	=	↓ 20%
Premix (70/30, 75/25)	=	↓ 50%

Pre-operative patients with hyperglycemia (blood glucose values above the 180-220 mg/dl upper threshold) will need insulin dose corrections to minimize related electrolyte and volume abnormalities and optimize post-operative recovery. The decision as to whether insulin correction pre-operative should be administered via subcutaneous or intravenous route depends on both the length of the planned surgery and its complexity²⁰. For surgeries that are expected to last much longer than a couple of hours, or more complex operations, such as coronary artery bypass graft, organ transplant, or prolonged neurosurgical procedures, control of hyperglycemia with IV insulin infusions is preferred, with insulin rate adjustments based on hourly (or at the most Q2 hourly) blood glucose testing. If basal insulin replacement is continued in the perioperative period, then transitioning back to subcutaneous insulin coverage post-operative becomes much simpler. At Parkland, the Global Diabetes Program, in close collaboration with a multidisciplinary group composed of stakeholders from surgery, hospital medicine, anesthesia, pharmacy, nursing and information technology, is piloting a perioperative insulin protocol across treatment areas with the hope of standardizing the approach to insulin management for the surgical patient and improve the quality of care.

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Inpatient diabetes management general guidelines

Glycemic targets

Critical care: 140-180 mg/dl initially & 110-180 mg/dl if stable

Non-critical care: <140 mg/dl pre-meal and fasting & <180 mg/dl at any time

Estimating Initial Total Daily Dose of insulin (TDD)

Calculate 0.5 units/kg/day based on weight (use 0.3 u/kg/d if frail/elderly or CKD 4-5 equivalent)

Add all insulin taken by patient over 24 hour period (prescribed outpatient TDD)

Use one of the above or an average of both; if A1C close to target consider using outpatient TDD as initial starting dose

Convert 70/30 insulin to basal/bolus on inpatient admission

Basal/bolus insulin distribution

Basal = 50% of TDD is for basal replacement

Prandial/mealtime = 50% of TDD is then divided into three (3) meals per day [patient eating meals]

Supplemental/corrective = LOW scale (TDD<40), MEDIUM scale (TDD=40-80), HIGH scale (TDD>80); use the Rule of 1800 to confirm choice of corrective scale

Consider using supplemental/corrective scale insulin for $BG \geq 150$ mg/dl (patient eating or receiving enteral/parenteral nutrition) or if $BG \geq 200$ mg/dl (bedtime or patient NPO)

Blood glucose monitoring

Patient eating: QAC, QHS & Q3AM (if HS BG covered by supplemental/corrective scale)

Patient NPO or continuous tube feeds: Q4 hrs (if using aspart) or Q6 hrs (if using Regular insulin)

Converting 70/30 to basal bolus on admission

Add all 70/30 insulin doses over the course of the day to calculate the TDD. Distribute TDD into basal/bolus as described above.

IV to SQ insulin transition

Extrapolate the total insulin infusion for the past 24 hours (TDD) based on stable rate insulin infusion

Distribute extrapolated TDD into basal (50%) and bolus (50%) insulin replacement

If patient NPO administer basal replacement plus supplemental scale (hold prandial insulin until patient starts PO intake)

Enteral feeds

Calculate carbohydrate (CHO) intake for a specific time period (4, 6 or 8 hr segments)

Match insulin to CHO using a ratio of 1:10 to 1:15

Distribute insulin as aspart (Q4 hrs), Regular (Q6 hrs) or NPH (Q8-12 hrs) to cover tube feeds

Parenteral nutrition

Calculate CHO (dextrose) amount in entire bag of hyperalimentation

Match insulin to CHO using a ratio of 1:10-15

Corticosteroid induced hyperglycemia

Administer NPH insulin at the time of steroid administration as follows (based on prednisone equivalents & patient weight:

10 mg = 0.1 u/kg, 20 mg = 0.2 u/kg, 30 mg = 0.3 u/kg, ≥ 40 mg = 0.4 u/kg

Consider increasing prandial insulin coverage while on steroids

Other pearls

- On admission stop SUs, metformin or 70/30 insulin; may continue DPP-inhibitor, GLP-1 RA or TZDs if no contraindications (pancreatitis, GI symptoms, fluid retention)
- Assess patient's home glycemic control: treatment type, A1C level, hypoglycemia frequency/severity
- For non-insulin treated patients, start insulin therapy if fasting BG>140 mg/dl or random BG>180 mg/dl
- Always place all patients with type 1 diabetes on basal insulin replacement (unless starting IV insulin infusion)
- May give basal as NPH BID, glargine daily or glargine BID (gets to steady state in 1.5 versus 3 days)
- May start basal insulin replacement 24-48 hours prior to planned transition from IV to SQ insulin (use IV insulin as a supplemental scale)
- Review recent A1C and start discharge planning for home diabetes management soon after admission

Inpatient diabetes management references & additional reading

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