

# A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic

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## **Abstract**

The pandemic of COVID-19 has presented new challenges to hospital personnel providing care for infected patients with diabetes who represent more than 20% of critically ill patients in intensive care units. Appropriate glycemic management contributes to a reduction in adverse clinical outcomes in acute illness but also requires intensive patient interactions for bedside glucose monitoring, intravenous and subcutaneous insulin administration, as well as rapid intervention for hypoglycemia events. These tasks are required at a time when minimizing patient interactions is recommended as a way of avoiding prolonged exposure to COVID-19 by health care personnel who often practice in settings with limited supplies of personal protective equipment. The purpose of this manuscript is to provide guidance for clinicians for reconciling recommended standards of care for infected hospitalized patients with diabetes while also addressing the daily realities of an overwhelmed health care system in many areas of the country. The use of modified protocols for insulin administration, bedside glucose monitoring, and medications such as glucocorticoids and hydroxychloroquine that may affect glycemic control are discussed. Continuous glucose monitoring systems have been proposed as an option for reducing time spent with patients, but there are important issues that need to be addressed if these are used in hospitalized patients. On site and remote glucose management teams have potential to provide guidance in areas where there are shortages of personnel who have expertise in inpatient glycemic management.

## Case of critical COVID-19 pneumonia in diabetes

A 60-year-old male with an 8-year history of type 2 diabetes, hypertension, hypercholesterolemia, and obesity (BMI 34 kg/m<sup>2</sup>) presented to the emergency room (ER) with high fevers and shortness of breath following two days of sore throat, dry cough, general fatigue, and diarrhea. He denied any recent travel history or known sick contacts. His home medications included metformin XR 2000 mg, glipizide 5 mg, irbesartan 150 mg, and atorvastatin 40 mg (all taken once daily in the morning). He denied a history of smoking, recent travel or known sick contacts. At presentation, he was in mild respiratory distress, with temperature 100.7°F, heart rate 100/min, blood pressure 142/95 mm Hg, respiratory rate of 22/min, and oxygen saturation of 94%.

Initial laboratory investigations revealed mild leukocytosis ( $11.4 \times 10^3/\mu\text{L}$  (normal range,  $4-10 \times 10^3/\mu\text{L}$ ), a low absolute lymphocyte count ( $0.7 \times 10^3/\mu\text{L}$  (normal range,  $1.1-3.2 \times 10^3/\mu\text{L}$ )), creatinine at 1.1 mg/dL (baseline 0.8 mg/dL), and a random blood glucose (BG) of 212 mg/dL (11.8 mmol/L). An HbA1c done the month prior to admission was 7.6% (60 mmol/mol). His electrolytes and liver function tests were normal. Real-time reverse transcription polymerase chain reaction (RT-PCR) assay on a nasopharyngeal swab was positive for SARS-CoV-2. Chest radiographs revealed bilateral infiltrates.

The patient was admitted and started on azithromycin and hydroxychloroquine. His home diabetes medications were discontinued and he was started on glargine insulin with a correction insulin scale prior to meals. Point of care blood glucose (POC BG) levels ranged between 140 and 210 mg/dl. Two days after the admission, he experienced worsening hypoxia. He was placed on 50% FIO<sub>2</sub> and transferred to the ICU where he was placed on mechanical ventilation due to worsening respiratory failure and hypotension.

## Background

The pandemic of COVID-19 has presented new challenges to hospital personnel providing care for these patients. This is particularly true for patients with diabetes, who represent 25 to 34% of the patient population receiving care in intensive care unit (ICU) and non-ICU settings and for whom appropriate glycemic management may contribute to a reduction in adverse clinical outcomes (1-4). Attention to glycemic management reduces morbidity and mortality in hospitalized patients with diabetes or newly recognized hyperglycemia with acute illness, including those with the SARS and COVID-19 virus (3,5-7). If left untreated, hyperglycemia increases risk for infections by altering leukocyte function and increasing the virulence of some pathogens; enhances risk for cardiac arrhythmias; prolongs hospital length of stay; and increase mortality (5,8). Implementation of protocols to control BG levels while also avoiding hypoglycemia have the ability to reduce these adverse outcomes (8-10).

Current recommendations for inpatient glycemic management include frequent monitoring of bedside BG together with structured insulin regimens. Insulin regimens composed of long acting and short or rapid acting insulin preparations are recommended for achieving glycemic targets of 100-180 mg/dl in non-critically ill patients (5,6). Intravenous (IV) insulin infusions are recommended for achieving glycemic targets of 140-180 mg/dl in critically ill patients (5,6,11). The ability to safely achieving these goals in the current environment has been viewed as problematic as glycemic management requires frequent patient interactions at a time when limiting these encounters is recommended, particularly in areas where there are shortages of personal protective equipment (PPE). These conflicting challenges have resulted in frequent queries from hospital personnel as to how to meet recommended standards of care for hospitalized patients with diabetes infected with SARS-CoV-2 while also addressing the daily realities of an overwhelmed health care system in many areas of the country.

Some suggested methods for limiting exposure time for health personnel when caring for patients with COVID-19 includes minimizing the use of IV insulin infusions in critically ill patients, using remote continuous glucose monitoring devices (CGM) devices to minimize time spent in direct patient contact, and reconsidering use of non-insulin therapies. In addition, the role of diabetes self-management by patients with diabetes in the hospital has gained renewed interest (11-14). Many hospitals are implementing strategies for limiting patient interactions, some of which may be achieved at risk of more hyperglycemia (15).

The purpose of this communication is to provide guidance for clinicians managing hospitalized patients with COVID-19 and diabetes or newly recognized hyperglycemia while also addressing the needs for protecting personnel who interact with these patients (16). It should be noted that much of this discussion will not be based on randomized controlled clinical trials for patients with COVID-19, but is instead extrapolated and modified from prior evidence-based guidelines for inpatient glycemic management as well as from the clinical experiences of several of the authors providing care to these patients. It is generally recommended that hospitals not make major changes to their current approach to managing hospitalized COVID-19 patients with hyperglycemia due to concerns that this alone can increase risk for unintended consequences requiring more time at the bedside. However, there are important and emerging issues that directly affect established glycemic management that warrant discussion and consideration during this pandemic (16).

### **Patients with COVID-19 Who May Not Require Scheduled Insulin Therapy**

Two groups of patients may fall into this category, those with well-controlled non-insulin treated type 2 diabetes and those with newly recognized hyperglycemia, defined as verified BG > 180 mg/dl (10 mmol/L). These patients require POC BG monitoring with initial use of correction

insulin to achieve and maintain BG between 100 and 180 mg/dl (5.5-10 mmol/L). Measurement of an HbA1c on admission helps identify patients with previously undiagnosed diabetes (17). Serum fructosamine, glycated albumin, and 5-andydro-glucitol may be more effective at determining glycemic status in patients with new hyperglycemia or those for whom HbA1c measures may be unreliable (e.g. thalassemia) (18). However, these measures have not been well studied in hospitalized patients (19). Decisions regarding use of home diabetes medications in those with type 2 diabetes can be based on type of medication and a patient's overall clinical status (Table 1) (See discussion on non-insulin therapies).

Patients with persistent POC BG < 180 mg/dl (10 mmol/L) for 24-36 hours following admission can have the frequency of glycemic monitoring decreased to once or twice a day with discontinuation of correction insulin. Patients with persistent elevations in BG > 180 mg/dl will require initiation of scheduled insulin therapy as discussed in the next section.

Any decision to stop glucose monitoring in high risk COVID-19 patients needs to be revisited for abrupt changes in clinical status or initiation of medications (glucocorticoids) or for nutrition support that can be associated with changes in glycemic status (20,21).

### **Patients with COVID-19 Who Require Insulin Therapy**

There are several methods for achieving desired glycemic goals while minimizing nursing time with COVID-19 patients that can be applied to patients in non-critical care and critical care areas. Hospital protocols vary in policies for types of patients treated in these areas, as well as allowing or disallowing IV insulin infusions in non-critical care areas (5,6,11).

Hospitalized patients with COVID-19 who have type 1 or insulin treated type 2 diabetes, as well as many patients on non-insulin agents prior to admission, and with persistent BG > 180

mg/dl (10 mmol/L) will require regular glucose monitoring together with scheduled insulin therapy to achieve desired glycemic goals. Scheduled insulin therapy is defined as the use of a basal insulin administered preferably as a long acting insulin preparation (e.g. glargine U100), prandial insulin for patients who are eating or receiving supplemental enteral or parenteral nutrition, and correction insulin for BG above target range (Table 2) (5,6). All insulin treated patients require POC BG measures to guide any glycemic management strategy. Glucose monitoring is done before meals and bedtime for patients who are eating, or every 4 to 6 hours for patients who are not eating or who are receiving enteral or parenteral nutrition (21,22).

For patients who are eating regular meals, there are few studies investigating the contribution of nutritional intake to glycemic management (23). Recommendations for timing prandial insulin administration with meals can be challenging in hospitals that allow meals on demand (23). In one study, there were more frequent episodes of mild hypoglycemia but no other differences in glycemic measures between patients following a consistent carbohydrate meal plan compared to a patient controlled meal plan (24). Patients in the latter grouped had their menus monitored by nutrition services. Low carbohydrate snacks provided to patients between meals are recommended as a way of avoiding hyperglycemia.

Prior to the COVID-19 pandemic, IV insulin infusions were recommended for glycemic management in the majority of patients with critical illness (5,11). Acknowledging the need for intensive nursing intervention to monitor BG every 1-2 hours with frequent adjustments to insulin infusion rates, some institutions have successfully implemented protocols adapted from previous studies for scheduled SC insulin therapy (Table 2) (25,26). Others have adapted nontraditional insulin strategies from the literature including more frequently dosed intermediate-acting (e.g. NPH) or premix insulin preparations (e.g. 70/30 for patients who are eating or receiving continuous



enteral nutrition) to accommodate the higher insulin requirements observed in many patients with COVID-19 (27) (personal observations). When glycemic control cannot be achieved with SC insulin, there is a need to implement IV insulin infusion protocols alone or in combination with basal insulin (28). Using basal insulin during an IV insulin infusion can facilitate transition to SC insulin without rebound hyperglycemia.

To minimize nursing time at the bedside with IV insulin infusion protocols, some hospitals have decreased the frequency of glycemic measures to every 4 to 6 hours when infusion rates are stable. With recent allowances by the FDA for use of continuous glucose monitoring (GGM) devices during the period of the COVID-19 pandemic, some hospitals are using these for remote tracking of glycemic data (see CGM discussion below).

Use of extension tubing for placement of medication infusion pumps, including insulin, outside a patient room has been implemented in some hospitals. This allows procedures such as verifying insulin dose calculations or adjusting insulin infusion rates to be performed outside of the room. There are concerns as to whether this practice could increase risk for infections or accidents if tubing contacts the floor. Solutions for these concerns include use of slit plastic noodles over extension tubing, use of stickers or hangers to channel tubing around room and out the door, or blue pads placed along the floor.

It is important to note that insulin requirements can vary on a daily if not hourly basis in patients with critical COVID-19 infections where there is variability in insulin sensitivity over the course of the illness (29). Significant variability in both SC and IV insulin dosing from low to very high insulin requirements independent of therapy with glucocorticoids has been reported by those caring for these patients. Patients with pre-existing chronic kidney disease or who experience acute kidney injury as part of COVID-19 infection may be particularly sensitive to

insulin and risk for hypoglycemia (30-32). Use of vasopressors or glucocorticoids in varying doses can significantly affect insulin requirements as doses are adjusted over time. This requires close attention to abrupt changes in glycemic measures with need for ongoing adjustments to insulin therapy.

Clustered care, defined as coordinating tasks (POC BG monitoring, storing insulin with other medications in a secured bin in patient rooms, administration of insulin and other medications, meal delivery, and clinical assessment), is recommended in non-critical and critical care settings as a way of minimizing direct patient interactions. Administering meal related rapid acting insulin following a meal has been advocated for some hospitalized patients who have reduced food intake (33). However, this practice necessitates additional nurse time with a patient, and has not been consistently observed to reduce hypoglycemia events (34,35).

### **Noninsulin therapies in patients with diabetes and COVID-19**

Previously published guidelines recommend discontinuation of non-insulin medications and initiation of insulin therapy for patients with diabetes or newly recognized hyperglycemia at time of hospital admission (5,6,11). There are several more recent studies investigating the safety and efficacy of these earlier recommendations as well as use of non-insulin agents in the hospital (36,37). This emerging data for use of non-insulin therapies in the hospital setting will be addressed here in reference to COVID-19 patients (Table 1).

There are several small studies demonstrating safety and efficacy of the dipeptidyl peptidase 4 inhibitors (DPP4i) sitagliptin and linagliptin in selected inpatients with type 2 diabetes (38-41). In response to these earlier studies, some centers prescribe these agents for hospitalized patients with type 2 diabetes and milder degrees of hyperglycemia ( $BG \leq 180$  mg/dl [10 mmol/L])

in the recovery phase of COVID-19 infection provided there are no contraindications (history of pancreatitis or pancreatic tumors).

There are several important issues to consider with inpatient use of DPP4i. The DPP4 enzyme was identified as a co-receptor for the MERS-CoV but not SARS-CoV or SARS-CoV-2 (42,43). At this time, there is no data demonstrating either harmful or beneficial impact of these agents in patients with COVID-19 (42,44). The use of saxagliptin and alogliptin is not recommended due to concerns for an increase incidence of heart failure (HF) (45,46). It is important to note that all published trials using DPP4i in the inpatient setting were conducted in combination with correction insulin, and several in combination with basal insulin therapy. Due to the unstable nature of acutely ill patients hospitalized with COVID-19, DPP4i are generally not recommended.

There are major issues associated with use of other non-insulin therapies in the hospital (Table 1). Sulfonylureas and other insulin secretagogues need to be used cautiously if at all, and discontinued for patients with declining renal function, who are elderly, or receiving insulin therapy due to concerns of hypoglycemia (47). Metformin is contraindicated in patients with or at risk of acidosis, including those with hemodynamic instability, hypoxia, and/or severe renal impairment (48). In the absence of clinical trials supporting use of metformin in acutely ill patients, it is recommended that current guidelines for discontinuation of metformin in hospitalized patients with COVID-19 be followed (37,42). Thiazolidinediones have a slow onset of action and are associated with fluid retention, aggravating risk for HF, particularly in patients receiving insulin, and should not be used in this population. Initiating therapy with glucagon like peptide receptor agonists (GLP1RA) is generally not recommended in the acute care setting due to concerns for nausea and vomiting, particularly in patients who are not eating regular meals (49).

Several GLP1RA are now available as once weekly formulations, which means that many hospitalized patients will have this on board at time of admission. Similar to DPP4i, continued use of these agents is generally not recommended for acutely ill patients with COVID-19 due to the potential for abrupt deterioration in clinical status.

There has been an expanded use of SGLT2 inhibitors in the outpatient setting due to their beneficial effects on cardiovascular and renal outcomes in people with and without diabetes (50). This means that many patients will be on these agents at the time of hospitalization. There is no data guiding their use in the inpatient setting, but the association of medications in this class with risk for euglycemic diabetic ketoacidosis (euDKA) and volume depletion contraindicates their use in any inpatient at this time (51,52). Consideration for stopping these agents in outpatients who become ill with COVID-19 is recommended given that glucosuria continues for several days following discontinuation, increasing risk for euDKA (53).

In summary, insulin therapy remains the standard of care for management of hyperglycemia in patients hospitalized with COVID-19. Selected use of the DPP4i, sitagliptin and linagliptin, can be considered for patients with type 2 diabetes or milder degrees of hyperglycemia once they are eating regular meals and discharge to home is anticipated. Patients receiving sitagliptin require monitoring of renal function with adjusted doses for renal insufficiency (40). At this time, despite the extensive publications demonstrating CVD and renal benefits with use of SGLT2i, these agents require discontinuation on admission (or even earlier) for any patient with COVID-19 due to concerns for euDKA, infection and hypovolemia.

### **Continuous Glucose Monitoring (CGM) Devices vs. Bedside Blood Glucose (BG) Monitoring**

Bedside BG monitoring using POC glucose meters remains the standard of care in hospitalized patients, despite identified issues relating to accuracy and precision of several of these

devices (11,54). The increased use of CGM devices in outpatient settings has led to significant improvements in glycemic control and variability with high levels of acceptance among individuals with insulin treated diabetes (55,56). Two devices approved for outpatient use in the US do not require calibration with capillary BG measures and offer the ability to remotely monitor BG data for up to 14 days depending on the device used.

On April 1, 2020, the FDA announced they would not object to in-hospital use of CGM to assist with monitoring COVID-19 patients following prior guidance (reported March 20, 2020) approving non-invasive remote monitoring devices for use in the hospital setting during this pandemic (57). Manufacturers of the Freestyle Libre (Abbott) and Dexcom G6 CGM devices notified the medical community that these devices would be provided at reduced cost during the pandemic, leading many institutions to adopt or consider adopting use of these devices in hospitalized patients with COVID-19.

There are no CGM devices that are approved for inpatient use. Of the several small trials (5-13 patients) using these devices in non-critical care areas, major findings include a decrease in frequency of and time spent in hypoglycemia (58,59). In another trial of ten surgical patients with diabetes, a correlation coefficient of 0.76 was observed between glycemic data obtained with a Dexcom G6 and POC BG measures performed over an average time period of 62 hours (60). It should be noted that these studies were conducted following extensive training and education of nursing personnel involved in these projects. Several studies using different CGM devices in critical care areas have demonstrated reductions in nurse time at the bedside, with some but not all studies demonstrating reductions in time spent in hypoglycemia but not mean BG (61,62). Importantly, the majority of prior studies did not use devices currently allowed by the FDA.

CGM offers a potential way for facilitating care in COVID-19 patients while also decreasing nurse exposure through reduced frequency of POC BG testing. The DEXCOM G6 allows glycemic data to be remotely transmitted to a receiver located outside a patient room as well as to computers at a nursing station.

It is important to note that manufacturers of the two CGM devices with temporary FDA allowances recommend against using sensor data for making treatment decisions related to insulin therapy (61). A POC BG is recommended for decision-making purposes for insulin dosing. Until there are studies validating their safety and efficacy in acute care setting, these CGM devices should be viewed as a supplement to and not a replacement for POC BG monitoring. CGM may be useful for monitoring of trends in glycemic data in some patients with alerts for hypoglycemia and hyperglycemia. Guidelines for POC BG testing in insulin treated patients should continue to be followed, with premeal and bedtime measurements in patients who are eating and every 4 to 6 hours in those who are not eating or are receiving supplemental nutrition.

If a decision is made by an institution to use CGM during this pandemic, there is a need for awareness of associated concerns and limitations before widespread implementation (61,62). There are important infrastructure issues that are required for safe implementation of these devices that include appropriate staff education and support for the technical aspects of the system. Physicians, advanced practice providers (APP), Certified Diabetes Care and Education Specialists, and nurses with expertise in placement and use of CGM devices can help establish protocols for CGM use and insulin dosing, as well as for monitoring device accuracy (63). Another important issue is integrating results from a CGM device with the electronic medical record (EMR), including nursing documentation (64). Health care personnel are working under a high level of

stress in many hospital settings where introduction of new and unfamiliar technologies may create an added burden.

The accuracy of CGM can be diminished during the conditions of altered tissue perfusion as well as use of certain medications and substances. Interference with accuracy of glycemic measures has been observed in patients receiving dopamine, heparin, salicylic acid, ascorbic acid, hydroxyurea, or high doses of acetaminophen (> 1000 mg every 6 hours) (61). Exposure to radiologic procedures including magnetic resonance imaging (MRI), computed tomography (CT) scanning, or even routine X-rays can potentially damage sensor components again leading to inaccurate glycemic measures. CGM devices need to be discontinued if there is potential for exposure to high-frequency electrical heat (diathermy) treatment. It is recommended that these devices be discontinued with placement of a new device if these procedures are performed, raising costs associated with use of these devices in the hospital setting.

Non-critically ill patients using CGM as outpatients may be permitted to continue these devices as inpatients if the same considerations relating to radiologic procedures and use of certain medications that can potentially interfere with results are followed. Some hospitals have protocols in place for individuals using these monitoring devices in the non-critical care hospital setting (61,62).

### **Diabetes Self-Management**

Diabetes self-management, defined as allowing selected patients to monitor BG and administer their own insulin, may be appropriate for patients who are knowledgeable, competent and clinically stable (11,14). Patients using continuous subcutaneous insulin infusion (CSII) therapy prior to admission are often inappropriately instructed to discontinue this at time of hospital admission (65-68). Patients treated with CSII assessed as competent to continue this in

the hospital setting need to provide their own pump supplies including infusion sets, cartridges, reservoir syringes and batteries. Many CSII patients own systems that integrate with CGM. There are currently two products that allow insulin adjustment based on algorithms that “learn” glucose patterns. Questions have been raised as to whether these hybrid closed loop insulin systems (Medtronic 670G, Tandem’s Control IQ program), are appropriate for use in the inpatient setting. In light of the reports of high glycemic variability during COVID-19 and treatment, and especially rapid decline in insulin needs that can occur with improvement, it is recommended that these programs be disabled. For those who continue using their hybrid closed loop system, hospital protocols should be followed to prevent untoward misadventures as can occur when exposed to an electromagnetic field, radiation or some medications (discussed above).

Patients assessed as being able to self-monitor POC BG and administer their own insulin using CSII or insulin injections need to do so according to hospital procedures and guidelines that require reporting of glycemic data and insulin dosing to nursing personnel who can record this in the EMR. These policies typically indicate that insulin dose calculations and administration be overseen by nursing personnel.

Patients may self-monitor BG levels using their own home BG meter, or a meter provided by the hospital. In the latter case, the meter is restricted to use only by one individual patient. In addition to recent guidance regarding inpatient CGM use, the FDA has recognized that home BG meters may be used by some hospitalized patients with diabetes and COVID-19 (69).

It is essential that non-critically ill patients performing self-management be reassessed several times a day given observed rapid deteriorations in clinical status with COVID-19 (2). Patients using CSII therapy who experience a deterioration in their clinical condition requiring transition to SC or IV insulin therapy will need to have these devices removed and given to a



family member or placed in a secured area until this can be returned to the patient. The infusion catheter for the device also needs to be removed from the skin to avoid a potential source of infection.

### **Special issues in Patients with COVID-19 Infection and Diabetes**

There are multiple drug therapies being studied using unique investigative strategies for determining optimal therapies for treating COVID-19 patients (70). Of these, systemic glucocorticoid therapy and hydroxychloroquine are agents with divergent but significant impact on glycemic control in patients with and without diabetes.

#### **Glucocorticoid Therapy:**

Glucocorticoids used in some mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome can aggravate hyperglycemia in patients with known diabetes and precipitate hyperglycemia in previously normoglycemic patients (71-73). Hydrocortisone dosed as 50 mg IV every 6 hours is a proposed investigative strategy for treating patients with COVID-19 (70). This dose is associated with hyperglycemia in patients with and without a history of diabetes (20,71). The management of patients with glucocorticoid induced or aggravated hyperglycemia poses specific challenges depending on the agent, dose, and frequency of administration.

Several different approaches to mitigating hyperglycemia associated with glucocorticoid therapy include administration of NPH insulin alone or in combination with basal bolus insulin regimens, or intensification of existing basal bolus insulin regimens (74,75). The pharmacokinetics of NPH insulin coincide with those of prednisone and methylprednisolone, making this an attractive alternative for managing hyperglycemia in patients receiving these therapies. Protocols using intensified basal bolus insulin regimens alone or in combination with NPH insulin have also been demonstrated as being effective in patients receiving longer acting glucocorticoids such as dexamethasone (76). An accompanying

continuous IV insulin infusion may become necessary for patients with persistent glucocorticoid-induced hyperglycemia if glycemic control is not achieved with SC insulin (30,72,77). To avoid variability in insulin requirements with glucocorticoid therapy in patients already being treated with an IV insulin infusion, some institutions administer hydrocortisone as a continuous infusion over a 24-hour period for patients in critical care areas (78).

### Hydroxychloroquine

Hydroxychloroquine is an agent under investigation for COVID-19 that has relevance to glycemic management (20). In one small trial, therapy with hydroxychloroquine resulted in improved beta cell function and insulin sensitivity in obese subjects with insulin resistance but without diabetes (79). In a systematic review of 18 studies with 55,776 participants, substantial reductions in were observed for HbA1c, fasting and postprandial plasma glucose levels. Insulin dose reduction by ~30% may be required for some patients receiving hydroxychloroquine to avoid hypoglycemia (80,81).

### Other medications

There are other medications used in hospitals (as well as outpatient settings) for patients with diabetes who are infected with COVID-19 that can affect blood glucose levels. An example of this would be the use of antitussive syrups containing glucose that can contribute to hyperglycemia.

### **Diabetes Inpatient Services**

Given the number of patients hospitalized with COVID-19 who also have diabetes or hyperglycemia, any inpatient diabetes service can be quickly overwhelmed with requests for consultation for glycemic management. In general, non-critically ill patients who have persistent BG < 180 mg/dl do not require subspecialty consultation. Both IV and SC insulin therapy can be

initiated for patients with persistent BG > 180 mg/dl according to hospital or published guidelines (5,6) (Table 2).

Glucose management teams may still need to be involved in the care of many patients with COVID-19, including those using CSII or who present difficult glycemic management issues despite implementation of guidelines described above. This can often be performed in the context of an e-consult or virtual telemedicine consult, with the goal of minimizing the number of personnel coming into direct contact with any one patient (82,83).

Some institutions have implemented virtual Glucose Management Services (vGMS) that collate glucose, insulin, nutrition and medication information in the EMR for remote review by a diabetes management team who makes remote recommendations to the primary team for adjustments in therapy (82,83). Implementation of a vGMS with daily suggestions for patients with elevated POC BG values resulted in a nearly 40% decrease in percentage of patients with hyperglycemia (83). For COVID-19 patients with glycemic management issues, a vGMS could be adapted to an active patient Dashboard to allow remote monitoring with suggestion for interventions as needed (84).

### **Discharging Patients with Diabetes and COVID-19 from the Hospital to Home**

Many but not all patients with diabetes hospitalized with COVID-19 infection will be knowledgeable regarding self-management at home. Even those who were previously comfortable with home management may be discharged with a different regimen than they were using prior to admission (85). Diabetes education and training is a key part of comprehensive diabetes care and should remain a part of discharge planning in the COVID-19 pandemic (85). Continuing to take advantage of technology, delivery of patient education can continue using telehealth with a HIPPA

compliant platform using tablets, computers, or smart phones (86,87). Bluetooth enabled pen devices can allow remote monitoring of compliance with timing and dosing of insulin regimens and identify patients who are at risk for uncontrolled diabetes (88). All self-management education should begin well before the day of discharge. Patients new to insulin should have the opportunity to practice self-administration using devices (vials and syringes, pen devices) they will use at home. Patients need to know how and when to take their diabetes medications, monitor POC BG levels, adjust therapy for low or high BG values, and who to contact in the event of glycemic emergencies. All patients discharged home with insulin or an insulin secretagogue need to know the symptoms and treatment of hypoglycemia events. For patients receiving basal bolus insulin therapy, a prescription for nasal or injectable glucagon provides reassurance that they will have appropriate tools in the event of a severe hypoglycemic reaction.

### **Back to the patient case**

Following transfer to the ICU and intubation, the patient was started on IV insulin using a protocol targeting BG values of 140-180 mg/dl (7.8-10 mmol/L). Over the next 24 hours, he required approximately 3 units/hour to maintain BG in this range. To address nurse concerns regarding frequency of BG monitoring with IV insulin requiring additional PPE each time they entered the patient room, he was transitioned to SC basal insulin at a calculated dose of approximately 50% of the 24-hour infusion dose (89,90). This was administered as glargine U100 36 units 2 hours prior to discontinuation of IV insulin. Correction doses of rapid acting aspart insulin were administered every 4 hours for POC BG > 140 mg/dl (7.8 mmol/L). Nurses clustered insulin administration and BG monitoring with clinical assessments and administration of other medications.

Enteral nutrition was eventually started with the addition of nutritional doses of aspart insulin every four hours. Nurses were instructed to hold scheduled aspart dosing if enteral nutrition was stopped (Table 2). The patient was eventually extubated with discontinuation of enteral nutrition and resumption of regular meals. His oral intake was initially low prompting reductions in doses of prandial and basal insulin. By day 14, his total daily insulin dose was 12 units allowing discontinuation of scheduled insulin. His serum creatinine returned to his baseline value of 0.8 mg/dl. Metformin therapy was resumed with initial continuation of correction insulin which was discontinued when all POC BG were <150 mg/dl (8.3 mmol/L). He was discharged home on metformin 1.5 G per day with plans to follow-up with his primary care physician.

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Table 1: Considerations for Non-Insulin Therapies in the Hospital Setting for COVID-19 Patients

Drug Class	Concerns for Hospital Use	Relevance to COVID-19 Patients
Sulfonylureas Insulin Secretagogues	High risk for hypoglycemia particularly in patients $\geq$ age 65, with eGFR $\leq$ 30 ml/min, or receiving insulin therapy	The occurrence of any hypoglycemic event increases need for interaction with hospital personnel.
Metformin	Contraindicated for patients with respiratory problems and hypoxia, hemodynamic instability, and unstable renal or hepatic function	Hospitalized patients with COVID-19 can experience sudden and rapid deteriorations in clinical status which contraindicates continued use of metformin in these patients when hospitalized
DPP 4 Inhibitors	DPP 4 enzyme has been identified as a co-receptor for the coronavirus which has potential to either favorably or unfavorably affect the binding of the virus to cell membranes. Majority of inpatient studies with these agents used these in combination with correction or basal insulin.	Generally not recommended in acute phase of COVID-19 due to concerns for abrupt deteriorations in clinical status. Saxagliptin and alogliptin should not be used as they are associated with higher risk for HF.
SGLT2 Inhibitors	Increases risk for euglycemic DKA, UTI, genital infections, and volume depletion	Discontinuation of these agents recommended at time of hospitalization.
GLP1 Receptor Agonists	Nausea and vomiting, particularly in patients who are not eating meals on a regular basis	Patients treated with long acting agents will have these on board at time of hospital admission. Continued use not currently recommended during acute hospitalizations.
Thiazolidinediones	Delay in glucose lowering effect, increase risk for fluid retention in insulin treated patients	These agents should not be used in this population.

Table 2: Initiating Insulin Therapy in the Acute Care Setting\*

	Basal Insulin	Prandial Insulin	Correction Insulin
Patients who are eating	Glargine U100 Starting dose: 0.1-0.2 units/kg/day**	Rapid acting analog 0.1 unit/kg/day in divided doses before meals	Administered prior to meals Reduce dose by 50% if given at bedtime
Patients who are NPO	Glargine U100 Dose: 0.1-0.2 units/kg/day	None	Administered every 4 to 6 hours as a rapid acting insulin analog or regular insulin, respectively
Patients receiving parenteral nutrition	Start if BG > 180 mg/dl despite use of insulin in TPN solution	1 unit/10 to 15 grams of carbohydrate in parenteral solution	Administered every 4 to 6 hours as a rapid acting insulin analog or regular insulin, respectively
Patients receiving continuous enteral nutrition <sup>‡</sup>	NPH insulin administered every 8-12 hours with rapid acting or regular insulin administered every 4 to 6 hours Or Human 70/30 insulin administered every 8 to 12 hours Starting dose: 0.1-0.2 units/kg/day**		
	Alternative regimen: Glargine U100 Starting dose: 0.1-0.2 units/kg/day	Administer as rapid acting insulin analog or regular insulin every 4 to 6 hours according to duration of enteral nutrition <sup>¶</sup>	Administered as a rapid acting insulin analog or regular insulin every 4 to 6 hours, respectively
Patients receiving bolus enteral nutrition <sup>‡</sup>	Administer rapid acting or regular insulin prior to administration of enteral nutrition (similar to patients eating meals). Some patients may also require basal insulin		Administered prior to bolus

\*Insulin doses require daily (or more frequent) adjustments to achieve glycemic goals without hypoglycemia

\*\*Patients with diabetes and COVID-19 will likely require higher insulin doses based on the severity of the underlying insulin resistance. Many may require well over 1 units/kg/day of insulin during acute phase of illness. There are some patients, such as those with chronic kidney disease or who experience acute kidney injury who may require lower insulin doses to avoid hypoglycemia.

¶ The dose of prandial insulin will vary according to the type of formulation used. For patients with diabetes, a starting dose of 1 unit for every 15 to 20 grams of carbohydrate administered over 24 hours

could be calculated and administered in divided doses as a rapid acting insulin analog or regular insulin. For patients with new hyperglycemia, a correction insulin scale could be used initially to determine the need for ongoing scheduled prandial insulin coverage.

<sup>±</sup> Insulin requirements may be lower in patients receiving low carbohydrate enteral nutrition formulations (Reference #20). In the event of abrupt discontinuation of enteral nutrition in insulin treated patients, a 10% dextrose infusion administered at the same rate is recommended for the duration of the longest acting insulin administered prior to discontinuation (Reference 6).

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