



Inpatient Hyperglycemia Management and COVID-19

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ABSTRACT

Diabetes is one of the most common comorbidities in hospitalized patients with coronavirus disease 2019 (COVID-19). Inpatient hyperglycemia during this pandemic has been associated with worse outcomes, so it is mandatory to implement effective glycemic control treatment approaches for inpatients

with COVID-19. The shortage of personal protective equipment, the need to prevent staff exposure, or the fact that many of the health-care professionals might be relatively unfamiliar with the management of hyperglycemia may lead to worse glycemic control and, consequently, a worse prognosis. In order to reduce these barriers, we intend to adapt established recommendations to manage hyperglycemia during this pandemic in critical and noncritical care settings.

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Key Summary Points

Diabetes is one of the most common comorbidities in hospitalized patients with coronavirus disease 2019 (COVID-19).

Inpatient hyperglycemia during the COVID-19 pandemic has been associated with worse outcomes, but improvement of glycemic control can reduce complications associated with hyperglycemia.

Effective glycemic control treatment approaches for inpatients with COVID-19 are needed while, at the same time, limiting the exposure of healthcare professionals. An individualized approach adapting the established recommendations for the management of hyperglycemia in hospitalized patients may reduce the barriers during COVID-19 pandemic.

DIGITAL FEATURES

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INTRODUCTION

Diabetes is one of the most common comorbidities of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The prevalence of diabetes among people affected by COVID-19 is not higher than that observed in the general population, suggesting that diabetes does not increase the risk of SARS-CoV-2 infection, but can worsen the outcome of the disease [1, 2]. In fact, clinical studies have

found diabetes to be a major risk factor for disease severity and mortality [3, 4]. Patients with diabetes and/or uncontrolled hyperglycemia are more than twice as likely to be admitted to intensive care units (ICU) and mortality is up to three times higher compared to patients without diabetes and/or uncontrolled hyperglycemia [5].

It is well established that inpatient hyperglycemia, with or without known diabetes, contributes to a significant increase in morbidity, mortality, length of hospital stay, and healthcare costs, and that better glycemic control improves clinical outcomes [6–8]. This was also evident in prior coronavirus infection outbreaks like the severe acute respiratory syndrome (SARS) [9].

Several mechanisms have linked hyperglycemia to the worse prognosis of COVID-19. These mechanisms include those related to hyperglycemia and glycemic control as well as the impaired immune and inflammatory response caused by hyperglycemia [10]. Poor glycemic control has been associated with worse outcomes, including higher resource utilization, prolonged length of hospitalization, multi-organ injuries, and higher mortality [10–13]. Hyperglycemia in patients with and without diabetes can also have a negative impact on the efficacy of COVID-19 therapies, such as tocilizumab [14]. Frequent comorbidities associated with diabetes, such as obesity and hypertension, have also been associated with poor prognosis [15]. However, a recent study has shown that diabetes is associated with poor early outcomes among hospitalized patients with COVID-19, after adjustment for obesity [16]. In addition, accelerated respiratory deterioration has recently been identified as another mechanism whereby hyperglycemia can lead to worse outcomes of COVID-19 [17].

While some of these mechanisms remain to be elucidated, it seems clear that optimizing glycemic control can be crucial to improve COVID-19 outcomes. Well-controlled blood glucose (BG) levels, defined as BG between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) have been associated with reduced medical interventions, major organ injuries, and all-cause mortality [11]. In fact, for every 10 mg/dL

(0.6 mmol/L) drop in glucose levels between admission and 18 days, an 11% relative decrease in severe disease risk has been described in patients with hyperglycemia [10].

The limited data available suggest that glycemic control in patients with COVID-19 is inadequate. An observational study that evaluated glycemic control among hospitalized patients with COVID-19, diabetes, and acute hyperglycemia described 39.1% of BG values above 180 mg/dL (10.0 mmol/L) and 37.8% of the time of admission spent with a mean BG above 180 mg/dL (10.0 mmol/L) [12]. Another study showed 56.6% of capillary BG tests above the recommended target of 140–180 mg/dL (7.8–10.0 mmol/L) [18]. This may be due to high levels of stress, inflammation, a cytokine-mediated insulin-resistant state and lack of adequate protocols for glucose management [19]. It is also possible that the SARS coronavirus can penetrate into pancreatic islets and damage beta cells leading to insulin deficiency, thereby aggravating the course of diabetes and triggering acute hyperglycemia even in people without diabetes [20, 21]. This is supported by the observation of frequent cases of ketosis and severe diabetic ketoacidosis (DKA) at the time of hospital admission [22]. On the other hand, a rather large number of hypoglycemic episodes at hospital admission have also been reported, probably favored by COVID-19-induced anorexia without concomitant adaptation of glucose-lowering drugs [18, 20]. There are other factors associated with BG fluctuation that are especially relevant in patients with diabetes and COVID-19, such as the use of glucocorticoids, that can lead to large glycemic excursions which should be considered in setting the insulin pattern [23].

In addition, healthcare workers can face challenges that need careful attention. Specialists from all disciplines may have to manage patients with COVID-19 outside of their usual specialty areas and, therefore, clinicians relatively unfamiliar with managing hyperglycemia may be required to do so [24]. The shortage of personal protective equipment and the need to prevent healthcare workers' exposure can also hinder glycemic control in patients with COVID-19.

In this clinical scenario, there is an urgent need to implement effective glycemic control treatment approaches for inpatients with COVID-19 [25]. However, no data is available regarding the most appropriate management of hyperglycemia in patients infected by SARS-CoV-2. Until then, given the aforementioned challenges, we intend to adapt established recommendations to manage hyperglycemia during this pandemic in critical and noncritical care settings. In Table 1 we summarize the main recommendations for the management of hyperglycemia in critically ill and noncritically ill patients with COVID-19 according to their clinical situation. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

MANAGEMENT OF HYPERGLYCEMIA IN CRITICAL PATIENTS WITH COVID-19

Glycemic Targets

Glycemic control goals in the ICU have been the subject of debate during the past 2 decades. It is generally accepted that intensive glycemic control [80–110 mg/dL (4.4–6.1 mmol/L)] compared to moderate control [140–180 mg/dL (7.8–10.0 mmol/L)] does not provide any benefit and in fact can increase the risk of hypoglycemia and even mortality [26, 27]. There is agreement that glucose levels above 180 mg/dL (10.0 mmol/L) may increase the risk of hospital complications. However, the lower limit for glycemia target is less well established and values greater than 110 mg/dL (6.1 mmol/L) are generally recommended in order to minimize the risks of hypoglycemia [7]. The GLUCOCABG study showed a significant reduction in complications among patients undergoing coronary artery bypass graft surgery without diabetes comparing a glucose target of 100–140 mg/dL (5.6–7.8 mmol/L) to a target of 141–180 mg/dL (7.8–10.0 mmol/L) [28], and the results of Krinsley et al.'s study in critically ill patients support a BG target of 80–140 mg/dL

Table 1 Hyperglycemia management in critically and noncritically ill patients with COVID-19

| | Glycemic targets | Clinical situation | | Insulin regimen | BG monitoring |
|----------------------------|--------------------------------------|-------------------------------|---|---|--|
| Critically ill patients | 140–180 mg/dL* (7.8–10.0 mmol/L) | Hemodynamically unstable | | Continuous intravenous insulin infusion | Every hour |
| | | Parenteral nutrition | | | |
| | | Unstable insulin requirements | | | |
| | | Corticosteroid therapy | | | |
| Noncritically ill patients | 110–180 mg/dL** (6.1–10.0 mmol/L) | T1D | Not oral intake | Basal-correction | Every 4–6 h ^{##} |
| | | T2D on oral agents ± insulin | Oral intake | Basal-bolus-correction | Before meals and at bedtime ^{##} |
| | | T2D on diet | Glycemia at admission < 180 mg/dL (10.0 mmol/L) | Correction insulin before meals or every 6 h [#] | Before meals and at bedtime or every 6 h ^{##} |
| | | Unknown DM | Glycemia at admission > 180 mg/dL (10.0 mmol/L) | Basal-bolus-correction | Before meals and at bedtime ^{##} |

BG blood glucose, T1D type 1 diabetes, T2D type 2 diabetes, DM diabetes mellitus

*110–140 mg/dL (6.1–7.8 mmol/L) may be reasonable for selected patients, as long as it can be achieved without significant hypoglycemia

**110–140 mg/dL (6.1–7.8 mmol/L) may be reasonable for stable patients with mild disease and previous tight glycemic control. BG levels > 180 mg/dL (7.8 mmol/L) might be acceptable for patients who are at high risk of hypoglycemia or who have limited life expectancy

[#] To calculate insulin requirements during the first 24 h. Then intensify to a basal-correction or basal-bolus regimen

^{##} Consider the use of continuous glucose monitoring if feasible to limit fingersticks

(4.4–7.8 mmol/L) for patients without diabetes and with diabetes when HbA1c is less than 7% (53 mmol/mol), but 110–160 mg/dL (6.1–8.9 mmol/L) in those with HbA1c levels of at least 7% (53 mmol/mol) [29]. Also deserving attention is the fact that glycemic variability per se has been associated with higher mortality rates than hyperglycemia in septic patients [30]. It has therefore been suggested that glycemic variability has to be part of the management of hyperglycemia, even in ICU patients [31]. These

data, like those established for outpatient diabetes management, support a potential benefit of a personalized glycemic target in critically ill patients.

Clinical guidelines recommend maintaining glucose levels between 140 and 180 mg/dL (7.8–10.0 mmol/L) for most critically ill patients [32] and more stringent goals of 110–140 mg/dl (6.1–7.8 mmol/L) may be reasonable for selected patients, as long as they can be achieved without significant hypoglycemia [7, 28, 29]. In

accordance with Pasquel et al. [33], we consider that these recommendations could be extended to critical patients with COVID-19.

Insulin Therapy

Insulin should be the treatment of choice for critically ill patients with COVID-19. The main aims of a safe and effective insulin regimen should be to reduce contact frequency, reduce glucose variability, minimize risk of severe hypoglycemia, and improve overall glycemic control [34]. As a result of the stress caused by SARS-CoV-2 infection and other factors, such as continuous tube feeding in patients on artificial ventilation and the risk of hypoglycemia when tube feeding is interrupted, or the use of high doses of corticosteroids, patients may suffer from great glycemic excursions [34]. To achieve glycemic targets, continuous intravenous insulin infusion, based on validated written or computerized protocols, is the most effective method [7, 35, 36]. The protocols that do not need a calculation of insulin doses (printed with decision columns and computerized protocols) are preferable to those that require calculations to decide the dose. Training of physicians and especially nurses in the efficient use of the protocol as well as predefining adjustments before important changes in BG and/or situations in which corticosteroids, vasopressors, parenteral nutrition, etc., are removed or added is important for protocol safety. However, the main factor that contributes to the safety of the protocol is the frequency of glycemic monitoring. The majority of insulin infusion protocols demand a minimum of hourly glucose monitoring for successful glycemic target achievement while reducing the risk of hypoglycemia. Checking glucose levels with a meter and test strips requires caregivers to enter a patient's room. In order to minimize healthcare workers' exposure when managing hyperglycemia in critically ill patients with COVID-19, for hemodynamically stable patients who are not on parenteral nutrition or high-dose corticosteroids, we recommend that the use of subcutaneous basal-bolus-correction or basal-correction insulin regimens should be

considered instead of intravenous insulin infusion and check BG levels four times a day together with other nursing activities to reduce the need to enter a patient's room. Transfer from intravenous to subcutaneous insulin administration will be recommended when the patient is clinically stable [37, 38]. The initial dose of subcutaneous insulin administration at the time of transition can be determined as 60–80% of the insulin administered intravenously during the preceding 24 h. To avoid rebound hyperglycemia after transition, a sufficient duration of overlap with the insulin infusion and the subcutaneous insulin administration is required. Short-acting insulin can be administered 1 to 2 h and long-acting insulin 2 to 3 h prior to discontinuation of intravenous insulin administration.

MANAGEMENT OF HYPERGLYCEMIA IN NONCRITICAL PATIENTS WITH COVID-19

Glycemic Targets

The American Diabetes Association (ADA) proposes the range of 140–180 mg/dL (7.8–10.0 mmol/L) as a target level of BG for the majority of noncritically ill patients [39]. However, the ideal glucose goals for noncritically ill patients remain undefined, and current recommendations are based mostly on retrospective studies, clinical experience, and judgment [7].

Evidence regarding appropriate glycemic targets for hospitalized patients with COVID-19 is lacking. As mentioned before, BG levels maintained between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) have been associated with better clinical outcomes [11]. Premeal and fasting BG values below 140 mg/dL (7.8 mmol/L) with maximal random BG below 180 mg/dL (10.0 mmol/L) might be appropriate in stable patients with mild disease and previous tight glycemic control, while glucose levels above 180 mg/dL (10.0 mmol/L) might be acceptable in patients who are at high risk of hyperglycemia or who have limited life

expectancy, as a way of minimizing the risk of hypoglycemia [7].

Insulin Therapy

There are limited data available about the efficacy and safety of non-insulin agents in hospitalized patients, almost restricted to dipeptidyl peptidase 4 (DPP4) inhibitors [40–44]. These agents in combination with basal insulin may represent an alternative in patients with COVID-19 and mild to moderate hyperglycemia [33]. DPP4 inhibitors have also been suggested to have a protective effect on COVID-19 [45]. However, recent studies found no association between the use of DPP4 inhibitors before admission and COVID-19 prognosis [20, 46, 47]. Moreover, we still do not have data on their use in hospitalized patients with COVID-19, and they may not be available in many hospitals. The incorporation of non-insulin drugs expands the therapeutic options and consequently the complexity of the prescription, which can be especially difficult when clinicians are unfamiliar with managing hyperglycemia. Glucagon-like peptide 1 (GLP-1) receptor agonists could be an attractive option, but they may increase the risk of gastrointestinal side effects [48]. Metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors should be discontinued at admission, because of the risk of lactic acidosis and DKA, respectively [49]. Some authors hypothesized that SGLT2 inhibitors could be effective in patients with hypoxemia and interstitial lung edema due to SARS-CoV-2 infection [50, 51]. Experience with three hospitalized patients without diabetes has been reported, showing no beneficial effects with the use of SGLT2 inhibitors [50]. All other oral agents, such as sulfonylureas or thiazolidinediones, should also be discontinued at admission.

Insulin is still considered the most appropriate pharmacologic agent for effectively controlling glycemia in hospital. Several regimens have proven to be effective for achieving and maintaining glycemic control. Current clinical guidelines recommend basal-bolus insulin regimens as the standard care for hospitalized

patients with hyperglycemia and diabetes in noncritical care setting [32, 36]. There is no data regarding the most appropriate regimen for patients with COVID-19, but the importance of achieving good glycemic control is evident [10].

A lot of evidence supports the use of basal-bolus regimens in noncritically ill patients. Randomized clinical trials have shown that basal-bolus treatment improves glycemic control and reduces the rate of hospital complications compared with reactive, or sliding-scale, insulin regimens [8, 52]. Compared to premixed insulin (70/30 NPH/regular insulin), a basal-bolus regimen has shown comparable glycemic control, but significantly fewer hypoglycemic episodes in medical and surgical patients [53]. A basal plus regimen compared with a standard basal-bolus regimen in medical and surgical patients with type 2 diabetes treated with diet, oral antidiabetic agents, or low-dose insulin resulted in a similar improvement in glycemic control without differences in hypoglycemia [54]. As for the types of insulin, regimens using insulin analogues and human insulin result in similar glycemic control in the hospital setting [55]. However, NPH insulin-based basal-bolus regimens have been largely supplanted by insulins analogue because of a perceived lower risk of hypoglycemia and because NPH insulin usually cannot be administered once daily. There are limited data regarding the use of new basal insulin analogues in the hospital setting. A recent study comparing glargine U300 and glargine U100 in a basal-bolus regimen in general medical and surgical patients with type 2 diabetes resulted in similar glycemic control, but significantly lower rates of clinically significant hypoglycemia [BG below 54 mg/dL (3 mmol/L)] with the use of glargine U300 [56]. In line with this study, another recent study in people with type 2 diabetes insufficiently controlled with basal insulin and/or non-insulin antidiabetic drugs, the COBALTA trial, confirms the efficacy and safety of insulin glargine U300 during hospitalization. This study also demonstrates that therapy intensification at discharge with glargine U300 is an effective strategy, improving HbA1c by 1.6% at months 3 and 6 post discharge with an adequate safety profile and a high degree of treatment satisfaction [57].

On the basis of these results, an insulin regimen with basal, prandial, and correction components would be the preferred treatment for noncritically ill hospitalized patients with COVID-19 and good nutritional intake, and basal insulin or a basal plus correction for patients with poor oral intake or those in which oral intake cannot be ensured [32]. Prolonged use of sliding-scale insulin regimens as the sole treatment of hyperglycemia is strongly discouraged [32].

Insulin Therapy in Glucocorticoid-Induced Hyperglycemia

The use of glucocorticoid therapy can aggravate or precipitate hyperglycemia in hospitalized patients with COVID-19 with and without known diabetes [58]. Regarding the use of high doses of corticosteroids in these patients, some authors have described their experience adding NPH insulin in a dose of 20–30 units in the morning in addition to the current insulin regimen as an efficient strategy to minimize the impact of steroids on BG values [34]. In our experience, the best option is to add the calculated increase in insulin dose, considering body weight and glucocorticoid dose, to the patient's usual total dose, distributing it according to the usual insulin regimen and glucocorticoid schedule [23].

GLUCOSE MONITORING IN HOSPITAL IN PATIENTS WITH COVID-19

Maintaining an adequate glycemic control usually requires multiple daily glucose measurements, which can be a challenge in patients under strict isolation. The implementation of technology that minimizes staff exposure while maintaining standard of care for hospitalized patients with diabetes is essential [59].

The US Food and Drug Administration (FDA) recognizes that home-use BG meters may be used by patients with diabetes who are hospitalized because of COVID-19 to check their own BG levels and provide the readings to the

healthcare workers caring for them [60]. Nevertheless, a way to monitor BG remotely, from outside the isolated rooms, is required [59]. This could be achieved by using BG meters that transmit the data via Bluetooth to an app or to a cloud. However, the use of continuous glucose monitoring (CGM) might be the ideal way to monitor BG in patients with COVID-19. It would allow, on the one hand, remote monitoring; on the other hand, it would help to enable BG control with low variability in the intended target range [31].

Inpatient clinical trials have tested the accuracy, safety, and efficacy of CGM technology in hospital, in both critical and noncritical patients [61–63]. Some experiences have already been reported in noncritical patients with COVID-19 with type 1 and type 2 diabetes, with the use of Guardian Connect (Medtronic), with significant improvement in mean glucose levels in all patients [59]. The main challenges for the use of CGM in hospital include training healthcare workers, the need for calibration procedures with some CGM systems, and cost. There are some systems such as FreeStyle Libre or Dexcom G6 that do not require BG calibration, minimizing risk of staff exposure and burden. Recently, the FDA approved the use of both FreeStyle Libre and Dexcom for inpatient use during the COVID-19 healthcare crisis in noncritically ill patients, but not in the critically ill [64–66]. Both systems can securely transmit glucose measurement data to digitally connected devices. As far as we know, no experiences have been reported with the use of these two CGM systems in hospitalized patients with COVID-19.

Some issues should be taken into account with the use of CGM systems in patients with COVID-19. Hypoxemia and possible reduction in peripheral perfusion could interfere with the accuracy of interstitial glucose measurement, especially in critically ill patients [67]. Acetaminophen, a commonly used antipyretic in patients with COVID-19, can interfere with CGM readings in some systems and may cause a CGM to overestimate glucose [68] (not in FreeStyle Libre or Dexcom G6). Glucose values in patients wearing a device that may be impacted

by acetaminophen should be interpreted with caution.

Regarding ICU patients, the integration of computer-guided insulin infusion with CGM or further development of new automated insulin delivery systems may be ideal [33]. Data about the use of hybrid closed-loop insulin infusion systems in critically ill patients are scarce. However, two recent cases of type 1 diabetes in patients with COVID-19 using t:slim Control IQ hybrid closed-loop system have been described, with optimal glycemic levels and minimal variability [34]. However, we will have to wait for more data on its efficacy and safety in critically ill patients before we can recommend its use.

Both the use of CGM systems and the use of hybrid closed-loop insulin infusion systems would require specific protocols for guidance, as well as access to specialist care [69]. Having an endocrinologist on consult, even over the phone or virtually, could help with all the approaches proposed [19, 70].

CONCLUSIONS

Improvement of glycemic control can reduce complications associated with hyperglycemia in hospitalized patients infected by SARS-CoV-2. Effective glycemic control treatment approaches for inpatients with COVID-19 are needed while, at the same time, limiting the exposure of healthcare professionals. Although we do not yet have data regarding the optimal glycemic targets for inpatients with COVID-19, it is clear that extremes of BG can lead to poor outcomes, and that insulin is the most appropriate treatment for effectively controlling glycemia in hospital. A target glucose range of 110–180 mg/dL (6.1–10.0 mmol/L) may be appropriate for most critically and noncritically ill patients, individualized according to patient characteristics and clinical situation. A continuous intravenous insulin infusion and scheduled basal-bolus correction insulin are the preferred regimens for glycemic control in critically and noncritically ill hospitalized patients, respectively. An individualized approach adapting the established recommendations may reduce the

aforementioned barriers during the COVID-19 pandemic. The use of subcutaneous insulin regimens in clinically stable patients may facilitate the reduction of the number of BG controls and, therefore, the exposure of the staff. In the same way, the implementation of technology that allows BG remote monitoring could help to limit fingersticks to check BG and, consequently, minimize staff exposure. The FDA approved the use of both FreeStyle Libre and Dexcom for inpatient use during the COVID-19 healthcare crisis. Further research regarding the evaluation of these changes in care is warranted in order to adapt our protocols.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human

participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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