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Review

A guidance on diagnosis and management of hyperglycemia at COVID care facilities in India



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ABSTRACT

Background and aims: Diabetes and coronavirus disease 2019 (COVID-19) share a bidirectional relationship. Hyperglycemia occurring in the setting of either previously diagnosed or undiagnosed diabetes is known to be associated with poor outcomes. Here, we aim to provide a simple and practical guidance on the diagnosis and management of hyperglycemia in admitted patients with COVID-19.

Methods: The guidance is formulated based on experience of authors and relevant literature on the subject searched using Pubmed.

Results: Every patient admitted to a COVID care facility should be investigated for hyperglycemia using a combination of tests including capillary blood glucose, fasting plasma glucose and HbA1c. Oral glucose lowering drugs can be considered in patients with mild COVID illness who have mild hyperglycemia [pre-meal blood glucose of <180 mg/dl (10 mmol/L) and post-meal blood glucose of <250 mg/dl (13.9 mmol/L)] and no contraindication to the use of these agents. All patients with moderate-severe disease and/or hyperglycemia of greater severity should be initiated on insulin therapy. Hyperglycemia should be aggressively screened for and managed in patients receiving systemic glucocorticoids.

Conclusion: This document provides a broad overview on the diagnosis and management of hyperglycemia at COVID care facilities and should be useful to a wide range of healthcare personnel involved in care of patients with COVID-19.

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1. Introduction

Since the report of the first case from Wuhan, China in December 2019, the coronavirus disease 2019 (COVID-19) cases have surged worldwide, and affected more than 216 countries. The current global toll of COVID-19 stands at >80.7 million confirmed cases with >1.7 million fatalities [1]. The pandemic has tremendously challenged scarce healthcare resources in our country. At the time of writing, India has already reported >10.2 million confirmed cases of COVID-19, and stands only next to United States of America in terms of numbers of cases reported [2].

Diabetes has been reported to be a major comorbidity among patients with COVID-19. The pooled prevalence of diabetes among patients with COVID-19 was reported to 11.5% (95% CI, 9.5% to 13.4%) in a recent meta-analysis [3]. The meta-analysis also found that patients with diabetes were more likely to encounter severe COVID-19 [HR 2.11 (95% CI, 1.40, 3.19)]. Another recent meta-

analysis has reported that diabetes is not only associated with increased disease severity [OR 2.35 (95% CI 1.80, 3.06)], but also increased mortality [OR 2.50 (95% CI 1.74, 3.59)] [4]. Besides, fasting blood glucose (FBG) has been reported to be an independent predictor of mortality among patients with COVID-19 without a previous history of diabetes [OR: 3.99 (95% CI 2.71, 5.88) at FBG \geq 126 mg/dl; OR: 2.61 (95% CI 1.64, 4.41) at FBG 110–125 mg/dl; reference category FBG <110 mg/dl] [5]. Hospitalised patients with COVID-19 who have optimal blood glucose control (glycemic variability within 70–180 mg/dl) are likely to have 10-fold lower mortality, compared to those with poor blood glucose control (upper limit of glycemic variability >180 mg/dl) [6]. Adults diagnosed with diabetes during the COVID-19 outbreak have been reported to present with more severe glycemia compared to those diagnosed before the outbreak [7]. Given that India has a huge burden of diabetes, and nearly half of the patients with diabetes remain undiagnosed, the challenges for our healthcare system are

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enormous [8,9]. The need of the hour is to not only improve the care for patients with pre-existing diabetes, but also to actively screen for and aggressively manage patients with undiagnosed diabetes and stress hyperglycemia [10].

Previous reviews published in this journal and elsewhere have highlighted the following issues relevant to COVID-19: a) relationship between COVID-19 and diabetes/other comorbidities [11–14], b) appropriate diagnosis and management of diabetes and other endocrine disorders during the pandemic [15–21], and c) the evolving role of telemedicine consultations in the era of COVID-19 and its pitfalls [22,23]. Given the huge burden of COVID-19 in our country, expertise for close supervision of diabetes management may not always be available and treatment decisions may need to be taken by non-experts or healthcare personnel from a non-clinical specialty deployed in COVID facilities. This review aims to provide a simple and practical guidance on the diagnosis and management of hyperglycemia, including steroid induced hyperglycemia in COVID-19, which could be helpful to a broad range of healthcare personnel caring for such patients.

1.1. Screening and diagnosis of diabetes

Every patient admitted to a COVID care facility should be investigated for hyperglycemia on the day of admission itself (Fig. 1). We suggest performing a random glucose value with a reliable blood glucose meter (step 1) at the time of receiving or admitting the patient in the facility. If the capillary blood glucose value is ≥ 180 mg/dl, one should be suspicious of underlying diabetes/stress hyperglycemia. In step 2, we suggest monitoring pre-meal and 2-h post meal capillary glucose around the first major

meal consumed after the admission. If the pre-meal value is ≥ 140 mg/dl and/or post-meal value is ≥ 180 mg/dl, we suggest initiation of regular blood glucose monitoring (4–6 times a day). In step 3, we suggest sending a blood sample for fasting plasma glucose (FPG) estimation to a laboratory on the day following admission. If the facilities are available, glycated hemoglobin (HbA1c) measurement should also be considered. A value of FPG ≥ 110 mg/dl has been found to be associated with increased mortality, and warrants further monitoring of capillary glucose over the next two days [5] (step 2). Patients without a previous diagnosis of diabetes and a current HbA1c of $\geq 6.5\%$ should be classified as having undiagnosed diabetes, while those without known diabetes, but with documented in-hospital hyperglycemia and a HbA1c value of $<6.5\%$ should be classified as having stress hyperglycemia [24].

In a recent study by Mithal et al., of 210 hospitalised COVID-19 patients with abnormal glycemic parameters, 58 (27.6%) had either undiagnosed pre-existing diabetes or new-onset hyperglycemia requiring insulin. Notably, COVID-related outcomes were worst among patients with new-onset hyperglycemia ($n = 21$; median HbA1c of 5.9%) [25]. The goal of a stringent screening policy should therefore be to identify individuals with undiagnosed diabetes and stress hyperglycemia (or new-onset hyperglycemia) who are often missed and eventually fare poorly in terms of disease outcomes and mortality rates, compared to their counterparts with diagnosed diabetes [26–28].

1.2. Need for regular monitoring

The previous section detailed the glycemic assessment of an individual at the time of admission (and on a subsequent day) in

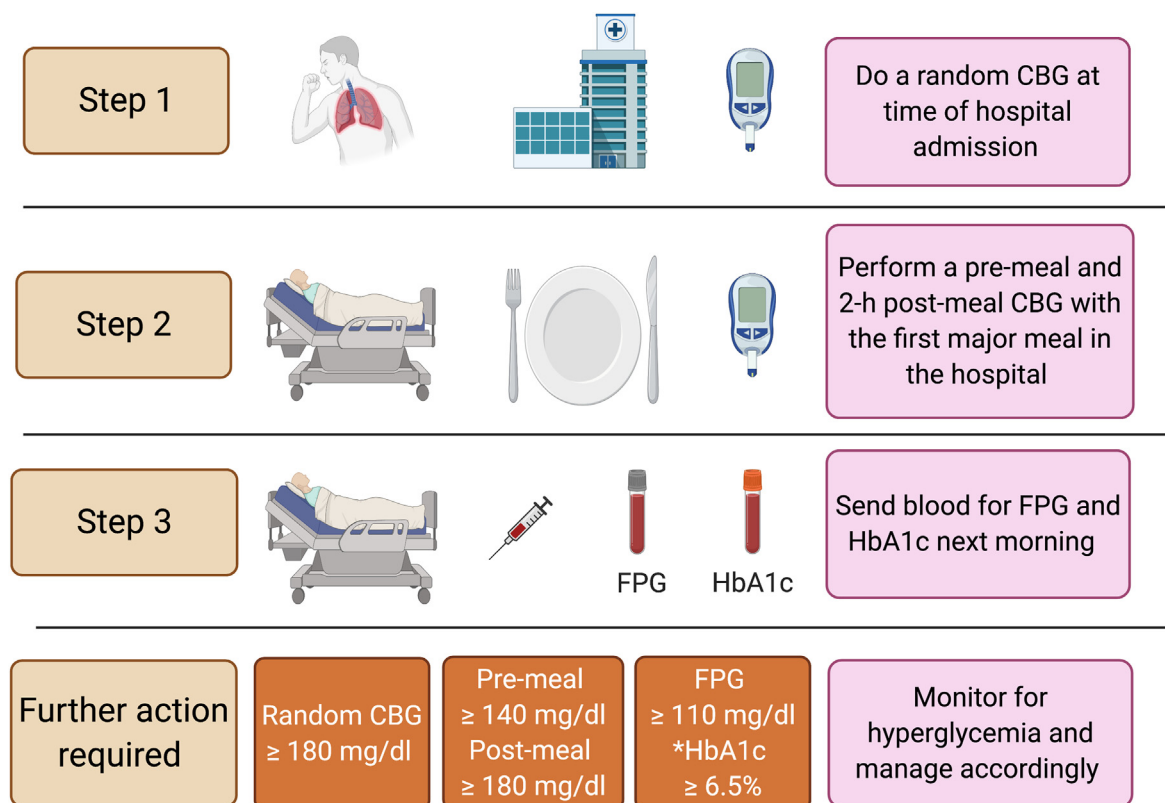


Fig. 1. A suggested algorithm for screening of hyperglycemia in patients admitted to a COVID care facility. *Patients without a previous diagnosis of diabetes and a current HbA1c of $\geq 6.5\%$ should be classified as having undiagnosed diabetes, while those without known diabetes, but with documented in-hospital hyperglycemia in face of a HbA1c value of $<6.5\%$ should be classified as having stress hyperglycemia. Abbreviations: CBG: Capillary blood glucose; COVID: Coronavirus disease 2019; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

order to uncover stress hyperglycemia or undiagnosed diabetes. However, we know that a patient with normal initial glycemic profile may develop stress hyperglycemia during the course of illness, especially if the individual moves up the COVID severity ladder. Besides, institution of glucocorticoids for treatment of primary disease may also contribute to hyperglycemia in such an individual [29,30]. Thus, glycemic assessment should be an ongoing dynamic process and not a one-time event (Fig. 2).

1.3. When can we continue oral glucose-lowering agents in a known case of diabetes?

According to the available guidance from multiple professional organizations, in general, insulin therapy should be preferred in hospitalised patients. However, considering the situation in our country, expert care may not always be available, and switching all patients on oral glucose-lowering agents to insulin may not be feasible. Therefore, in the absence of compelling indications for the use of insulin, we suggest that oral glucose-lowering agents can be continued. An ideal candidate would be one with mild COVID illness who does not have any contraindication for the continuation of oral drugs (such as renal or liver dysfunction), and has mild hyperglycemia (pre-meal blood glucose < 180 mg/dl and post-meal blood glucose < 250 mg/dl) (Fig. 3). The initiation of oral anti-hyperglycemic agents can be considered in patients with newly detected hyperglycemia (e.g., undiagnosed diabetes or stress hyperglycemia), who meet the above thresholds.

In line with other guidelines, we suggest stopping SGLT-2 inhibitors due to the risk of dehydration and euglycemic diabetic ketoacidosis [16]. We also suggest stopping pioglitazone due to its fluid retaining properties, which may be detrimental, especially in individuals on insulin, and those with myocardial dysfunction.

Metformin carries a risk of lactic acidosis in the presence of renal insufficiency, hypoxia, and hemodynamic instability, and should be discontinued if these conditions are present. Sulfonylurea (SU) cause blood glucose-independent insulin release, and can therefore result in hypoglycemia in patients with poor oral intake or erratic diet pattern. Considering their relative safety, dipeptidyl peptidase-4 (DPP-4) inhibitors can be continued, provided the patient has no underlying pancreatic disease [15,16]. In low resource settings like ours, vildagliptin and teneligliptin may be preferred over sitagliptin and linagliptin due to their low cost.

1.4. When to initiate insulin therapy?

We suggest initiation of insulin therapy in individuals with moderate to severe COVID due to its relative safety and efficacy. We also suggest insulin therapy if there is little possibility of achieving euglycemia in the short-term with initiation or up-titration of DPP-4 inhibitors, metformin, and sulphonylureas (e.g., pre-meal blood glucose of ≥ 180 mg/dl and post-meal blood glucose of ≥ 250 mg/dl). Finally, in patients with contraindications to the use of oral antihyperglycemic drugs, insulin treatment is mandatory. We suggest initiation of basal-bolus regimen (three injections of prandial and one or two injections of intermediate/long-acting insulin) or basal-plus regimen (prandial injection(s) for the meal(s) with more than desired postprandial excursion + basal injections) when pre-meal glucose values are ≥ 180 mg/dl and/or post-meal values are ≥ 250 mg/dl. We suggest initiation of continuous intravenous insulin infusion in individuals with severe hyperglycemia (pre-meal glucose values of ≥ 300 mg/dl and/or post-meal values of ≥ 400 mg/dl) and evaluation for ketosis at baseline (Fig. 4).

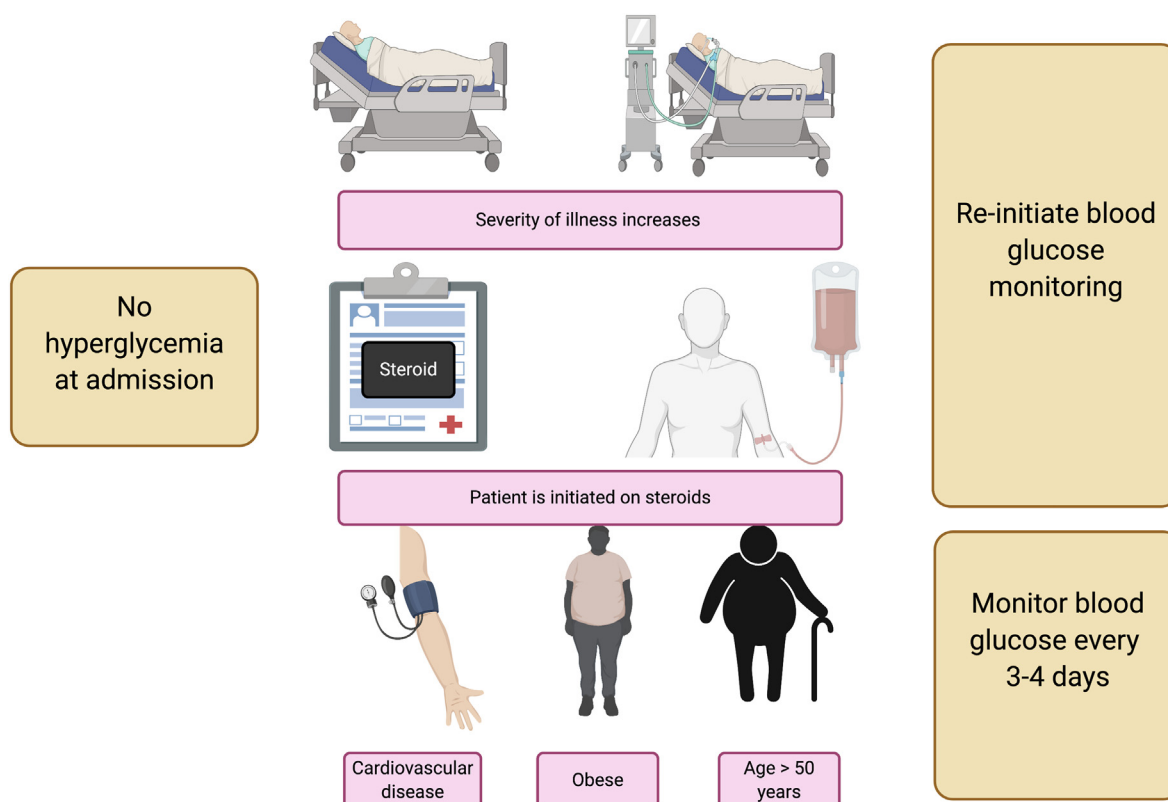


Fig. 2. Blood glucose monitoring strategy for individuals with no evidence of stress hyperglycemia or undiagnosed diabetes at the initial screen.

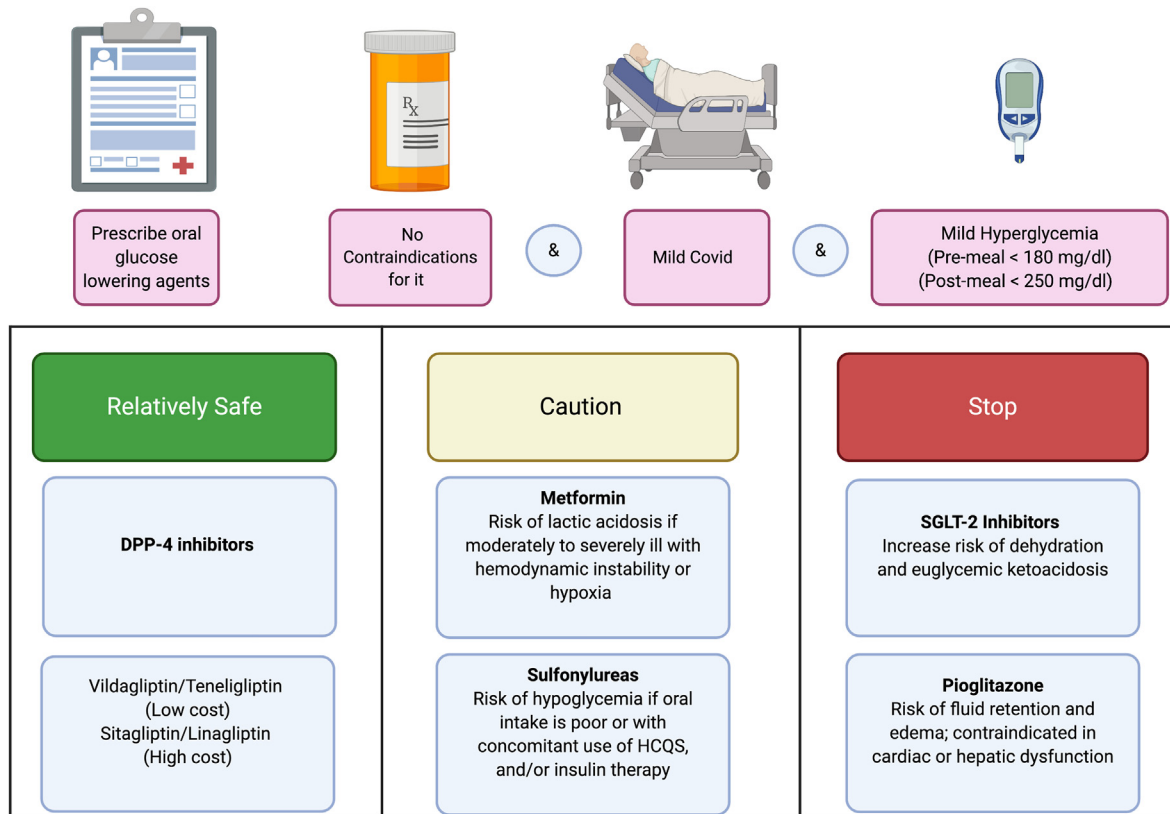


Fig. 3. Guidance on the use of oral glucose lowering agents in patients with SARS-CoV-2 infection. Abbreviations: COVID: Coronavirus disease 2019; DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors; HCQS: Hydroxychloroquine sulfate; SARS CoV-2: Severe acute respiratory syndrome coronavirus 2; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors.

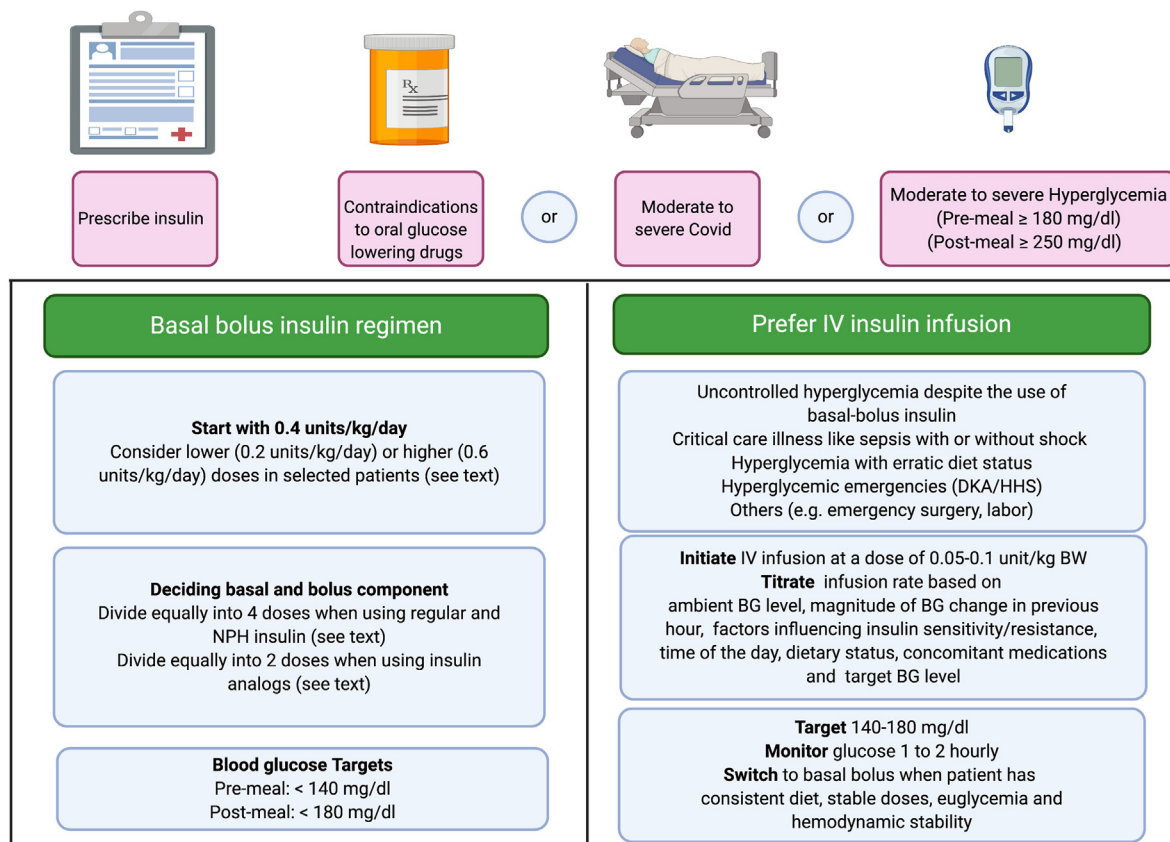


Fig. 4. Guidance on initiation of insulin therapy, use of basal-bolus insulin therapy and intravenous insulin infusion in patients with SARS-CoV-2 infection. Abbreviations: BG: Blood glucose; NPH: Neutral Protamine Hagedorn; SARS CoV-2: Severe acute respiratory syndrome coronavirus 2; SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar state; IV: Intravenous; BW: Body weight.

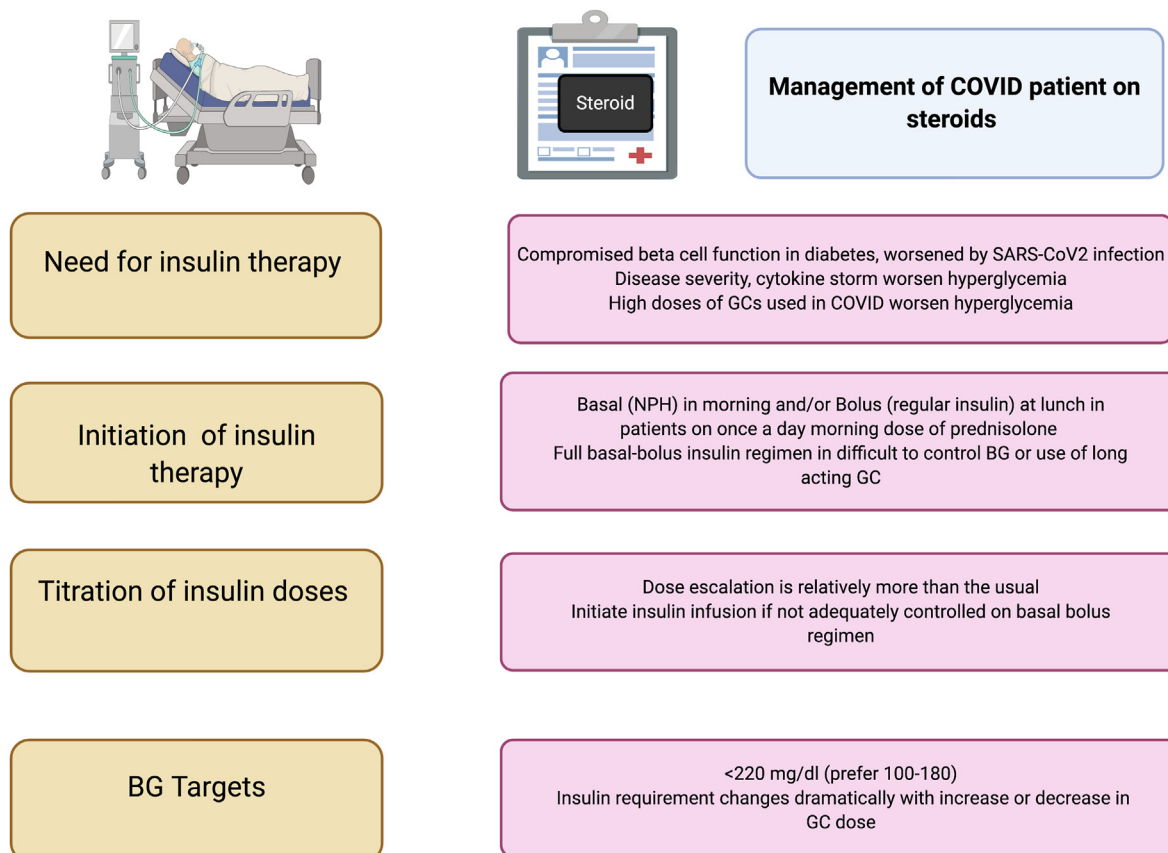


Fig. 5. Guidance on the management of glucocorticoid induced hyperglycemia in patients with SARS-CoV-2 infection. Abbreviations: BG: Blood glucose; COVID: Coronavirus disease 2019; GC: Glucocorticoid; SARS CoV-2: Severe acute respiratory syndrome coronavirus 2; NPH: Neutral Protamine Hagedorn.

1.5. How to manage patients on a basal-bolus insulin regimen?

Patient who were already on basal-bolus regimen prior to admission should be continued on the same and insulin doses should be adjusted according to blood glucose monitoring. For insulin naïve patients, insulin should be initiated at a dose of 0.4 units/kg/day (consider lower starting dose of 0.2 units/kg/day in elderly patients or those with liver or renal dysfunction), and administer it in four equal doses (one each for prandial coverage and one for basal coverage in a scenario where regular and intermediate-acting insulin are used) or two equal parts (one part for prandial coverage, further subdivided into three equal portions, and one part for basal coverage in a scenario where short and long acting insulin analogs are used) [17]. The initial dose can be higher, (e.g., 0.6 units/kg/day) in overweight/obese patients, or those who had a high pill burden before admission. The insulin dose should be titrated to achieve and maintain pre-meal glucose values of <140 mg/dl and post-meal glucose values of <180 mg/dl (Fig. 4).

1.6. How to manage a patient on insulin infusion?

Intravenous insulin infusion should be considered for patients who have uncontrolled hyperglycemia despite the appropriate use of a basal-bolus insulin regimen. Besides, insulin infusion should be the preferred modality in patients with erratic diet pattern or those with hyperglycemic emergencies such as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar coma. The infusion should be initiated at a low dose of 0.05–0.10 units/kg/hour, and the infusion rate should be titrated taking into account several factors

such as existing blood glucose level, magnitude of blood glucose change in the previous hour, desired blood glucose target, insulin sensitivity and the expected intake of a major or minor meal. A general target should be to maintain blood glucose between 140 and 180 mg/dl (Fig. 4).

1.7. How to manage hyperglycemia in patients on glucocorticoids?

Following the emergence of positive results from the RECOVERY trial [31], the use of glucocorticoids among patients with COVID-19, especially those with moderate-severe disease, has increased significantly. The use of high dose glucocorticoids is associated with an increased risk of hyperglycemia, which is often challenging to manage. Even patients who have previously well-controlled blood glucose levels may require large doses of insulin (e.g., >2 units/kg/day) to achieve glycemic control following initiation of glucocorticoids. For patients receiving twice daily intermediate acting glucocorticoids (e.g., methylprednisolone), it is best to start a basal-bolus insulin regimen. On the other hand, individuals who receive a single daily dose of intermediate acting glucocorticoid demonstrate disproportionately high blood glucose values in the afternoon and evening hours (before lunch, after lunch and before dinner), and may benefit with a single shot of prandial insulin before lunch, and/or an intermediate-acting insulin in the morning hours. It should be kept in mind that insulin doses may require rapid up-titration or down titration with an increase or decrease in glucocorticoid doses (Fig. 5). For patients with uncontrolled hyperglycemia despite the use of basal-bolus regimen, the use of intravenous insulin infusion should be considered.

1.8. Advice on discharge

Patients with diabetes who maintain their blood glucose levels with oral glucose-lowering agents during admission can be discharged on the same medications with advice for periodic follow-up. Patients who were on basal bolus insulin regimen and required relatively high doses (e.g., >1 unit/kg/day) should preferably be discharged on given insulin regimen itself, albeit with reduction in total insulin dose. On the other hand, individuals on insulin dose between 0.5 and 1 units/kg/day can be discharged on twice daily pre-mix insulin and oral glucose-lowering agents. Finally, patients who required only low doses of insulin (e.g., <0.5 units/kg/day) and no other medications to control hyperglycemia may be discharged on oral glucose-lowering agents like DPP-4 inhibitor, metformin, SUs, after careful consideration of drug safety. At discharge, the patient should be provided appropriate diabetes education, especially on diet, and lifestyle management, self-monitoring of blood glucose and hypoglycemia care. Patients discharged on insulin should be educated regarding injection technique, storage, blood glucose log maintenance, and dose adjustment based on blood glucose readings. The discharge summary should provide a detailed account of comorbid situations, advised medications, any specific instructions, and time for the next consultation which could be either in-person or telephonic.

2. Conclusion

This guidance document provides a broad overview on the diagnosis and management of hyperglycemia at COVID care facilities and should be useful to a wide range of healthcare personnel involved in care of patients with COVID-19.

Author contributions

YG, AG and NT conceived the idea of this paper. YG and AG wrote the first draft of the manuscript which was read and edited by SK, KG and NT. The figures were prepared by YG using paid prescription from [Biorender.com](https://www.biorender.com). All authors approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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