**Recommendations for Glycemic Treatment for Patients Receiving Dexamethasone for Treatment of COVID-19**

Ana Cristina García-Ulloa¹, José Luis Cárdenas-Fragoso², Óscar Arturo Lozano Cruz², Alfonso Gulías-Herrero², Sergio Hernández-Jiménez²

¹Centro de Atención Integral del Paciente con Diabetes (CAIPaDi) Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.
²Departamento de Medicina Interna. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

**Corresponding author:** Sergio Hernández-Jiménez, Vasco de Quiroga No. 15, Colonia Sección XVI, Tlalpan, Mexico. 14080, Tel: ±1 52 55 54870900 (5045); ±1 52 55 55737378; Email: sergio.hernandezj@incmnsz.mx


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**Abstract**

**Introduction:** SARS-CoV-2 infects not only cells of the upper respiratory system. Overproduction of proinflammatory cytokines results in cytokine storm, leading to hyper permeability, multiorgan failure, and death. The cytokine storm is more likely to develop in patients with uncontrolled diabetes. Dexamethasone reduces mortality in patients with COVID-19, but insulin resistance and hyperglycemia are common adverse effects which are also associated to worse outcomes.

**Methods:** We analyze and recommend treatment with insulin in patients with hyperglycemia treated with dexamethasone. Articles for review were selected including information with hyperglycemia caused by steroids. After analyzing the information and adhering to endocrinology guidelines, we propose an algorithm for treating patients hospitalized with COVID-19 and hyperglycemia (with or without diabetes) and require steroid treatment.

**Results:** It is important to consider the characteristics of each patient, specially weight, nutritional status, age, and renal function. Due to an increased insulin resistance, good control requires more bolus doses. A good approach is to start 50/50% of basal/bolus insulins.

**Discussion:** Steroids are the best treatment for patients with important inflammation. There are important factors to consider in these hospitalized patients to start insulin treatment, but also for discharge. Hyperglycemia in these patients can be approached by provision of insulin via basal and bolus insulin.

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**Keywords:** COVID-19; dexamethasone; hyperglycemia; diabetes; insulin

**Introduction**

SARS-CoV-2 affects epithelial cells from the upper respiratory system, but many other tissues have been involved in the disease. The affection of immune cells induces apoptosis of lymphocytes promoting severity of the disease. The activation of innate immunity causes lymphopenia and disables the suppression of immune response and cytokine secretion. The proinflammatory cytokines (10) causes a cytokine storm which is associated to vascular filtration, multiorgan failure and death [1].

Low-grade chronic inflammation is present in patients with uncontrolled diabetes. During viral infections, the immune response is compromised making them prone to severe adverse events. In previous epidemics (as SARS CoV1, MERS, influenza), hyperglycemia was an independent predictor for morbidity and mortality. This might be the same scenario for COVID-19 [1].

Recently, the RECOVERY collaborative Group reported that dexamethasone can reduce mortality in patients with COVID-19 who require invasive mechanical ventilation or supplemental oxygen therapy. Therefore, this steroid has been added to the treatment guidelines for COVID-19 [2].

One of the side effects of steroid treatment is the metabolic changes they cause, especially in serum glucose...
concentrations. In patients with diabetes, steroids can induce hyperglycemia by up to 56% [3]. In hospitalized patients receiving high doses of steroids, 86% have at least one episode of hyperglycemia and 48% of them usually have average blood glucose levels above 140 mg/dl [3].

Glucocorticoids cause hyperglycemia by several mechanisms [4,5]. They inhibit glucose uptake in muscle, increase hepatic gluconeogenesis and exert multiple effects on the receptor and post-receptor activity of the beta cell in the pancreas [5, 6]. The major hyperglycemic effect is mediated through increased insulin resistance in skeletal muscle. These effects promote hyperglycemia in “at risk individuals” (table 1). Steroids exacerbate hyperglycemia in patients with pre-existing diabetes and increase the likelihood of complications, length of in-hospital stay and mortality (4-7).

### Table 1: Insulin dose modifications according to glycemic control

For these conditions, specific measures should be considered for the detection and treatment of hyperglycemia in patients receiving dexamethasone due to COVID-19. The following are characteristics of patients who may present with hyperglycemia during treatment with dexamethasone:

- Patients with prior diagnosis of diabetes and people with abnormal fasting blood glucose or glucose intolerance
- Overweight or obese patients, family history of diabetes, prior diagnosis of gestational diabetes, polycystic ovary syndrome or acanthosis nigricans
- Patients with previous history of steroid-induced hyperglycemia.

#### Dexamethasone prescription.

It is recommended that dexamethasone be administered in the morning (around 07:00 a.m. - 08:00 a.m.). In this schedule, dexamethasone will cause hyperglycemia by late morning and can continue all day long. During the night, glucose falls back, normally to levels near basal. In any case, treatment must be adapted for each individual case hyperglycemia and avoid nocturnal hypoglycemia [8].

#### Glucose targets and monitoring.

Pre-meal target glucose level for inpatients is 100-140 mg/dl, while random levels should be <180 mg/dl [6]. Individualized targets with an appropriate care plan should be documented to facilitate treatment evolution [8].

An essential part in the care plan is performing Capillary Blood Glucose (CBG) monitoring. This will help drive correct therapeutic interventions. CBG should be measured at least 4-6 hours after administration of glucocorticoids [4]. Some recommendations include [3, 8]:

**Patients without pre-existing diabetes:**

- Monitor at least once daily (prior to lunch or evening meal), or 2 hours after lunch or evening meal. In case of glucose <180 mg/dl, continue monitoring once daily.
- If glucose is >180 mg/dl, increase monitoring to 4-times daily (before meals and at 22h)
- If glucose is consistently >180 mg/dl, change monitoring like a patient with diabetes.
- Since 94% of hyperglycemic cases appear within 2 days of starting steroid treatment in hospital setting, in patients without diabetes who continue with blood glucose levels below 140 mg/dl without insulin requirements for 48 hours, should not continue with glycemic monitoring [7].

**Patients with known diagnosis of diabetes**

- Monitor 4-times daily: before meals and at 22h.

#### Calculating insulin type and dosage

In patients on once-daily steroids, this should be administered in the morning (as previously commented) and add a basal dose of insulin (NPH, glargine or degludec) because of their similar pharmacodynamic properties [7, 8]. We suggest an increase between 10-20% of insulin dose, titrated to blood glucose level. Increments up to 40% might be required in special cases [7]. Other studies suggest starting with 0.3 - 0.5 units/kg [3]. Patients on treatment with corticosteroids, require a higher insulin dose in order to compensate peripheral insulin resistance [9].

There are different regimens that can be used to treat patients with insulin in case of hyperglycemia. Basal-bolus (BB) regimen has shown to be the most effective regimen for glucose control. This regimen is also associated with lower frequency of hospital complications than other regimens as the sliding scale insulin (SSI), without increasing severe hypoglycemic events [6, 9].

In India, Lakhani et al developed a new protocol incorporating “correctional insulin” depending on the glycemic profile of the glucocorticoid used. This protocol showed lower blood glucose and glycemic variability, with less episodes of severe hyperglycemia [10]. Pharmacodynamic profiles of insulins must be considered to match the corresponding profiles of glucocorticoids [5].

Dhital et al studied patients treated with prednisone and using a BB regimen (with glargine or NPH). All three studies showed...
similar glycemic control for NPH or glargine [5]. Both agents were equally effective as basal insulin to treat these patients, with a similar number of hypoglycemic episodes [6].

### Basal-bolus

BB is the preferred regimen for insulin treatment in hospitalized patients with diabetes [8, 9]. They also require more bolus doses for lunch and evening meal with short-acting insulin.

### Sliding Scale Insulin (SSI)

This regimen has the inconvenience that it has a fixed amount of insulin in the sliding scale does not prevent hyperglycemia. SSI can easily cause hyperglycemic crisis, resulting in worsening of medical conditions [9].

According to different articles, the following treatment algorithm is proposed for patients with diabetes who are hospitalized by COVID-19:

- Initiate with total insulin dose of 0.5 units/kg of weight per day.
- Initiate with total insulin dose of 0.3 units/kg of weight in lean patients, with malnutrition, > 65 years or with diminished estimated glomerular filtration rate (<60 ml/min/1.73m²). (12)
- Of the total calculated dose, use 50% of basal insulin (NPH, glargine, degludec) and 50% of rapid-acting insulin (regular, lispro, aspart or glulisine). Divide bolus into 3 doses: at breakfast, lunch, and dinner.

For example, a patient weighing 80 kg (overweight) would have 40 units of insulin total dose (80kg x 0.5U). Consider 20 units of basal insulin (NPH, glargine) + rapid insulin 7 units at breakfast, 7 units at lunch and 7 units at dinner. In total there were 41 units of insulin.

- Evaluate the scheme daily and apply necessary changes.
- If blood glucose levels are between 100 and 140 mg/dl, continue the same scheme.
- If the fasting glycemia of the next day is out of control goals, modify the dose according to table 1.
- If the preprandial blood glucose levels are out of the control target, add correction units (table 2)

<table>
<thead>
<tr>
<th>Preprandial glucose (mg/dl)</th>
<th>Short action insulin dose added per day</th>
<th>In patient example:</th>
</tr>
</thead>
<tbody>
<tr>
<td>141-180</td>
<td>+1</td>
<td>(7 + 1 each meal) 8-8-8</td>
</tr>
<tr>
<td>181-220</td>
<td>+2</td>
<td>(7 + 2 each meal) 9-9-9</td>
</tr>
<tr>
<td>221-260</td>
<td>+3</td>
<td>(7 + 3 each meal) 10-10-10</td>
</tr>
<tr>
<td>&gt;260</td>
<td>+4 Check ketones and consult with the endocrinologist</td>
<td>(7+ 4 each meal) 11-11-11</td>
</tr>
</tbody>
</table>

### Complications of Steroid Use

Hyperglycemia can occasionally cause acute complications such as hyperosmolar hyperglycemic syndrome or diabetic ketoacidosis and increase the risk of infections [4]. Many reports have shown a high prevalence of patients with COVID-19 who develop acute diabetes complications as diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome. The presence of these complications were associated with negative outcomes in these patients [1].

SARS-CoV-2 has a direct effect in pancreatic tissue, which might cause insulin deficiency. This effect, in addition to anorexia, cause elevation of ketones. Insulin deficiency and cytokine storm cause an important deterioration and makes of utmost importance the glycemic control [1].

### Management after Discharge

Patients with HbA1c >8% may benefit from intensification of their diabetes regimen at discharge. For patients on non-insulin agents before admission, consider prescribing insulin at discharge for the following patients: (11)

- Patients needing significantly more than 20 units of insulin per day during their hospital stay.
- Patients whose oral agents became contraindicated during the hospitalization (eg, changes in renal function).

Any diabetes medication adjustment must be accompanied by a close follow-up plan and provider contact information for any issues with BG management, as patients' BG can change rapidly within weeks of discharge. Several factors may affect BG levels after discharge. Patients with deteriorating renal function are prone to experience prolonged effects of insulin that might require dose reductions.

For new onset DM or new insulin treatment, patients will need additional formal diabetes education after discharge. Patients should have appropriate supplies at discharge as well. Provide anticipatory guidance about what to do in the event of high or low BGs after discharge. The guidance can be provided either as titration instructions or as call parameters with contact information for the appropriate physician.

In the discharge summary, providers should document any changes that were made to the diabetes medical regimen and identify the medical provider who will be responsible for outpatient diabetes management. Close follow-up should be arranged [11].

If the patient is discharged from hospital and still needs steroid therapy, it is important to explain a plan to manage possible hyperglycemia. Standard education is important for these patients, including [8]:

- Diabetes drug treatment
- Lifestyle changes
- Recognize and avoid factors associated with hyperglycaemia and hypoglycemia
• Continue monitoring glucose once daily, in different times of the day
• If dexamethasone dose remains for some additional days and the patient is treated with insulin, monitoring of capillary blood glucose should continue.
• Lower the dose of hypoglycemic drugs when the dose of steroids decreases.

If the patient is discharged without steroid treatment, but hyperglycemia persists, continue monitoring glucose levels and consider practicing a fasting glucose, OGTT or HbA1c. If the patient is discharged without steroid treatment and with normal glucose levels, there is no need to continue monitoring. A special case to consider is in patients without diabetes who experienced steroid induced hyperglycemia. For these patients, screening for diabetes should be undertaken 6 weeks after finishing steroid treatment.

Conclusion

Steroids are the best treatment for patients with important inflammation. As this, glucocorticoids have shown benefits in patients with COVID-19 and important respiratory distress. However, treatment with steroids worsen insulin resistance and glycemic control. BB regimen is the best approach to manage steroid-induced hyperglycemia since these patients have variable appetite. Basal and bolus insulin regimen is safe and also effective for inpatient management of steroid-exacerbated hyperglycemia in patients with diabetes.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contribution

Research idea and study design SCHJ; data acquisition: SCHJ, ACGU, JSCF, and OALC; data analysis/interpretation: all authors contributed equally; manuscript drafting: ACGU, JSCF, and OALC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

References