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Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes

The RECOVERY (Randomised Evaluation of COVid-19 thEraPy) trial found that dexamethasone 6 mg once per day for 10 days reduced deaths by one-third in ventilated patients and by one-fifth in other patients, receiving oxygen therapy. This equates to the prevention of one death in around eight ventilated patients, or one in around 25 patients requiring oxygen. This welcome news has been considered such an important therapeutic advance that the regimen has been fast-tracked in the UK even though the study has yet to attain peer review publication.

Although described by the investigators as ‘low dose dexamethasone therapy’ the dose is in effect five- to sixfold greater than the therapeutic glucocorticoid replacement dose. High doses of glucocorticoids exacerbate hyperglycaemia in people with diabetes, may unmask undiagnosed diabetes and, in those at risk of diabetes, may precipitate hyperglycaemia and new-onset diabetes (commonly termed ‘steroid-induced diabetes’). Furthermore, glucocorticoids are the commonest cause of people with diabetes developing potentially life-threatening hyperglycaemic hyperosmolar state (HHS) in hospital. To prevent these harms, the Joint British Diabetes Societies (JBDS) published guidelines on the management of inpatients with and without diabetes receiving steroid therapy.2 However, these guidelines, which have been adopted in most UK hospitals, may not be appropriate for those with severe COVID-19 infection receiving dexamethasone, given the additional impact of the disease on glucose metabolism. The ‘cytokine storm’ resulting from severe COVID-19 infection is associated with significant insulin resistance and reduced insulin production from the pancreatic β cells. This dual pathology can precipitate severe hyperglycaemia, life-threatening ketoacidosis and HHS in people with diabetes, and even in people without, diabetes.3

To prevent these harms, the UK National Diabetes COVID-19 response group published in this journal guidance on the management of COVID-19-related hyperglycaemia.4 However, given the ‘triple insult’ of dexamethasone-induced impaired glucose metabolism, COVID-19-induced insulin resistance and COVID-19 impaired insulin production, we now provide new guidance specifically for use in people with severe COVID-19 infection commencing dexamethasone (Figure 1). The aim is to ensure that all patients commenced on dexamethasone, whether or not they have diabetes, receive appropriate glucose surveillance and management of hyperglycaemia should it occur. The guidance informs the clinician of the key facts pertaining to this clinical situation and the reasons why these recommendations differ from the JBDS guidelines. It describes the frequency at which capillary blood glucose monitoring should be undertaken in those with and without diabetes and gives the target ranges of capillary blood glucose levels to aim for.

The guidance recommends giving correction doses of rapid-acting analogue insulin when capillary blood glucose > 12.0 mmol/l, with the dose calculated according to the patient’s weight or in those already treated with insulin, on their total daily insulin dose. The correction doses recommended are notably higher than those used in our previous hyperglycaemia guideline given the inevitable increase in insulin resistance. Unlike the previous guidance, we do not recommend using the insulin correction ratios that some people with type 1 diabetes usually use as these may not be appropriate given the significant disturbance of glucose metabolism.

To maintain glycaemic control we recommend using NPH insulin which has an intermediate duration of action in preference to longer-acting insulin even though the metabolic effects of dexamethasone can persist for up to 36 h. NPH insulin given twice daily allows more flexibility in dose adjustment. The starting doses based on weight are slightly greater than those given in our previous guidance but as before, a reduced dose should be used in the frail, elderly and those with an eGFR of < 30 ml/min. If the patient is already on a long-acting insulin or twice daily pre-mix insulin then it is recommended this be increased by 20%, but it is noted that this may actually require rapid escalation by 40% or more.5 Insulin resistance will fall when dexamethasone is stopped and so capillary blood glucose and insulin dose adjustment need careful monitoring to avoid hypoglycaemia. The guidance table for the NPH and long-acting insulin assists in dose escalation and down titration of these insulins.

Finally, close initial follow-up is advised for those with known diabetes and a yearly HbA1c measurement is recommended for those with steroid-induced hyperglycaemia.

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1. RECOVERY Trial Collaborative Group, G E et al. (2020) The RECOVERY trial: a randomised trial of dexamethasone in hospitalised patients with COVID-19. The Lancet 396: 1665-1675.
2. Joint British Diabetes Societies (JBDS). (2020) Management of inpatients with and without diabetes receiving steroid therapy. https://www.nice.org.uk/guidance/ng159
d3. UK National Diabetes COVID-19 response group. (2020) National Diabetes COVID-19 response group. https://www.diabetes.org.uk/coronavirus/
d4. UK National Diabetes COVID-19 response group. (2020) National Diabetes COVID-19 response group. https://www.diabetes.org.uk/coronavirus/
d5. UK National Diabetes COVID-19 response group. (2020) National Diabetes COVID-19 response group. https://www.diabetes.org.uk/coronavirus/
because this group have been shown to be at increased risk of developing diabetes at a later date.

We hope that these guidelines will be helpful for those managing patients with COVID-19 treated with dexamethasone in the ward setting. Although not intended for critical care units where policies around blood glucose monitoring may differ and where insulin is likely to be given by intravenous infusion, the guidelines may be adapted for use in this setting.
MANAGING DEXAMETHASONE RELATED HYPERGLYCAEMIA

First, exclude Diabetic Ketoacidosis and Hyperglycaemia Hyperosmolar Syndrome by checking blood glucose, ketones, venous pH, bicarbonate and U&Es and if DKA/HHS diagnosed follow specific guidelines for their management.

⚠️ If DKA/HHS have been excluded, follow the guidance below but note, this advice is conservative. If after initial treatment hyperglycaemia persists, do not hesitate to escalate to the next treatment step and involve the diabetes team as early as possible.

ADVICE FOR CORRECTING INITIAL HYPERGLYCAEMIA – GLUCOSE ABOVE 12.0 MMOL/L

Use subcutaneous rapid acting insulin analogue (Novorapid®, Humalog®/Apridra®) as described below. Note these are conservative doses and depending on response in individual patients, as previously stated, may need to be increased rapidly (or where more insulin sensitive, decreased).

Recheck glucose at 4 hrs to determine response and whether a further correction dose is needed.

- Insulin naïve
  - Follow the weight-based tables below in those people:
    - not known to have diabetes
    - with type 2 diabetes treated with diet alone or with oral hypoglycaemic agents

- Insulin treated
  - Where the total daily dose (TDD) of insulin is known follow the guidance in the table based on TDD. If the TDD is unknown, follow guidance according to the person’s weight.

CORRECTION DOSES OF RAPID ACTING INSULIN

| GLUCOSE (MMOL/L) | TDD = <50 UNITS PER DAY OR WEIGHT < 50 KG | TDD = 50 - 100 UNITS PER DAY OR WEIGHT 50 - 100 KG | TDD = >100 UNITS PER DAY OR WEIGHT >100 KG |
|------------------|------------------------------------------|-----------------------------------------------|------------------------------------------|
| 12.0 - 14.9      | 2 units                                  | 2 units                                       | 4 units                                  |
| 15.0 - 16.9      | 2 units                                  | 3 units                                       | 5 units                                  |
| 17.0 - 18.9      | 3 units                                  | 4 units                                       | 5 units                                  |
| 19.0 - 20.9      | 3 units                                  | 5 units                                       | 6 units                                  |
| 21.0 - 22.9      | 4 units                                  | 6 units                                       | 7 units                                  |
| 23.0 - 24.9      | 4 units                                  | 7 units                                       | 8 units                                  |
| 25.0 - 27.0      | 5 units                                  | 8 units                                       | 9 units                                  |
| Over 27          | 6 units                                  | 9 units                                       | 10 units                                 |

- Please check KETONES if glucose >12.0mmol/L
- If KETONE >1.5mmol/L, for doctor review
- If KETONE >3.0mmol/L
  - Exclude DKA-Venous pH, bicarbonate, lab glucose, U&.E. Refer to diabetes team

MAINTAINING GLYCAEMIC CONTROL

- People NOT on an intermediate acting (NPH) or long acting insulin:
  - Where glucose has arisen above 12.0 mmol/L due to dexamethasone treatment, start NPH insulin which has an intermediate duration of action (e.g. Humulin R*, Insulatard*)
  - Total dose 0.3 units/kg/day. Give 2/3 of the total daily dose in the morning (07.00 – 08.00) and the remaining 1/3 in the early evening (17.00 – 18.00), e.g. 0.3 x 80kg = 24 units/d (i.e. 16 units a.m. and 8 units p.m.).
  - NOTE: there should be a low threshold for dose escalation (see table below) and referral to the diabetes team.

NPH insulin twice daily is recommended as this gives more flexibility with dose adjustment. However, the metabolic effects of dexamethasone can persist for up to 36 hours, thus a longer acting basal analogue insulin may also be considered. See tables below for dose adjustment of long acting insulin and twice daily intermediate and long acting insulins.

⚠️ ALERT NOTE IF:

- Older (>70 yrs) or frail
- Serum creatinine >175 umol/L (eGFR <30 ml/min)

Use a reduced NPH insulin dose of 0.15 units/kg (e.g. 0.15 x 80kg = 12 units i.e. 8 units a.m. and 4 units p.m.)

- NOTE: there should be a low threshold for dose escalation and referral to the diabetes team.

- People already using once or twice daily long-acting insulin or twice daily NPH including those on basal-bolus regimens

Increase the long-acting basal or NPH insulin by 20% but this may need rapid escalation by as much as 40% depending on response. Titrate the dose using the tables below. Patients on basal-bolus regimens may not require ‘mealtimes’ insulin boluses if not eating, however, if hyperglycaemia persists during adjustment of basal insulin then use corrective rapid acting insulin doses according to total daily insulin dose (TDD) or weight given in the table for correction doses of rapid acting insulin.

FIGURE 1  Continued
DOSE ADJUSTMENT FOR LONG-ACTING INSULIN

Doses can be titrated daily, although longer-acting insulins may take 48-72 hours to reach steady state. Dose adjustments will affect blood glucose throughout the day.

ONCE daily long-acting insulin

| GLUCOSE LEVEL | JUST BEFORE INSULIN DOSE |
|---------------|--------------------------|
| <4mmol/L      | Reduce insulin by 20%    |
| 4.1-6mmol/L   | Reduce insulin by 10%    |
| 6.1-12mmol/L  | No change                |
| 12.1-18mmol/L | Increase insulin by 10%  |
| >18mmol/L     | Increase insulin by 20%  |

TWICE daily NPH or long-acting insulin

| GLUCOSE LEVEL | JUST BEFORE MORNING INSULIN DOSE | JUST BEFORE EVENING INSULIN DOSE |
|---------------|----------------------------------|---------------------------------|
| <4mmol/L      | Reduce evening insulin by 20%    | Reduce morning insulin by 20%   |
| 4.1-6mmol/L   | Reduce evening insulin by 10%    | Reduce morning insulin by 10%   |
| 6.1-12mmol/L  | No change                        | No change                       |
| 12.1-18mmol/L | Increase evening insulin 10%     | Increase morning insulin by 10% |
| >18mmol/L     | Increase evening insulin by 20%  | Increase morning insulin by 20% |

People using a personal insulin infusion pump

If the person is too unwell to manage their pump, transfer to a Variable Rate Intravenous Insulin Infusion (VRIII) with a basal insulin given alongside – seek the advice of the diabetes team. If the pump is removed, give the pump to a relative for safekeeping or label with the patient’s details and safely store.

These people well enough to manage their subcutaneous insulin infusion pump should be recommended to initially increase the basal rates by 20% and be made aware that this may need to be increased further on a daily basis. Refer all people using a personal insulin pump to the diabetes team.

END OF DEXAMETHASONE THERAPY - DAY 10

Insulin resistance will begin to fall when the dexamethasone has been stopped but may take a number of days. Continue to monitor glucose 6 hourly and down titrate using the guidance table above.

DISCHARGE AND FOLLOW-UP

Diabetes precipitated by COVID-19 infection and dexamethasone treatment

Normoglycaemia may be established after stopping dexamethasone without the need for ongoing diabetes therapy. However, up to a third of people may later develop diabetes therefore alert the GP that the patient will need a yearly HbA1c measurement.

People with known diabetes

These patients will require close support following discharge. The discharge guidelines and patient information leaflet produced by this group are available to facilitate this. The leaflet can be accessed here: https://www.diabetes.org.uk/professionals/resources/shared-practice/inpatient-and-hospital-care#patients

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REFERENCES
1. Low-Cost Dexamethasone Reduces Death by up to One Third in Hospitalised Patients With Severe Respiratory Complications of COVID-19. Available at https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19 Last accessed 6 July 2020.
2. Roberts A, James J, Dhatariya J. Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med. 2018;35:1011-1017.
3. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020;8:1011-1017.
4. Rayman G, Lumb A, Kennon B, et al. New guidance on managing inpatient hyperglycaemia during the COVID-19 pandemic. Diabet Med. 2020;37:1214-1216.
5. Dashora UK, Taylor R. Maintaining glycaemic control during high-dose prednisolone administration for hyperemesis gravidarum in type 1 diabetes. Diabet Med. 2003;21:297-301.