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Letter

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 [1]. 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 six6 fold 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-threating 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. 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 HbA_{1c} measurement is recommended for those with steroid-induced hyperglycaemia 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.

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FIGURE 1 Concise advice on inpatient diabetes.

COncise adVice on Inpatient Diabetes (COVID:Diabetes):

DEXAMETHASONE THERAPY IN COVID-19 PATIENTS: IMPLICATIONS AND GUIDANCE FOR THE MANAGEMENT OF BLOOD GLUCOSE IN PEOPLE WITH AND WITHOUT DIABETES

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

ABCD

NATIONAL INPATIENT DIABETES COVID-19 RESPONSE GROUP*

This guidance is for use in ALL patients with COVID-19 who are treated with dexamethasone in a ward setting

It is NOT intended for Critical Care Units but may be adapted for this use

It differs from the previous COVID: Diabetes GUIDANCE FOR MANAGING INPATIENT HYPERGLYCAEMIA as it targets the greater insulin resistance in dexamethasone treated patients and should ONLY be used in this context

Key Facts

- Dexamethasone reduces mortality in people with COVID-19 who require ventilation or oxygen therapy
- Corticosteroid therapy impairs glucose metabolism and is the commonest cause of life threatening inpatient Hyperglycaemic Hyperosmolar Syndrome (HHS)
- COVID-19 increases insulin resistance and impairs insulin production from the pancreatic beta cells; this can precipitate hyperglycaemia and life threating Diabetic Ketoacidosis (DKA) in people with diabetes and even in people not known to have diabetes
- Glucose levels above 10.0 mmol/L have been linked to increased mortality in people with COVID-19
- The recommended dexamethasone dose of 6mg/day (oral or IV) for 10 days, equivalent to 40mg of prednisolone/day, will undoubtedly affect glucose metabolism
- Thus, the **triple whammy** of dexamethasone induced impaired glucose metabolism, COVID-19 induced insulin resistance and COVID-19 related impaired insulin production could result in significant hyperglycaemia, HHS and DKA in people with and without diabetes, increasing both morbidity and mortality
- Sulphonylureas are NOT recommended in this context as beta cell function may be impaired and insulin resistance is likely to be severe. For this reason, these recommendations differ from those in the JBDS guideline on the Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy

AIMS

To ensure ALL patients on dexamethasone receive appropriate glucose surveillance and appropriate management of hyperglycaemia

GLUCOSE MONITORING

Target glucose 6.0 -10.0 mmol/L (up to 12.0 mmol/L is acceptable)

Frequency of monitoring

- **People not known to have diabetes**

  Check the glucose at least 6 hourly ideally at fasting periods (e.g. before meals and at bedtime). If after 48 hours all fasting glucose results are <10.0 mmol/L reduce frequency to once daily at 17.00-18.00 hrs. Continue until dexamethasone is stopped

  If any fasting glucose is above 10.0 mmol/L continue 6 hourly monitoring and follow the guidance below to correct hyperglycaemia i.e. glucose above 12.0 mmol/L

- **People with diabetes**

  Throughout the admission, check fasting glucose at least 6 hourly, or more frequently if the glucose is outside the 6.0 -10.0 mmol/L range

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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	• Please check **KETONES** if glucose >12.0mmol/L
15.0-16.9	2 units	3 units	5 units	
17.0-18.9	3 units	4 units	5 units	⚠ **If KETONE >1.5mmol/L, for doctor review**
19.0-20.9	3 units	5 units	6 units	
21.0-22.9	4 units	6 units	7 units	⚠ **If KETONE >3.0mmol/L** Exclude DKA-Venous pH, bicarbonate, lab glucose, U&E. Refer to diabetes team
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	

MAINTAINING GLYCAEMIC CONTROL

› **People NOT on an intermediate acting (NPH) or long acting insulin:**

Where glucose has risen above 12.0 mmol/l due to dexamethasone treatment, start NPH insulin which has an intermediate duration of action (e.g. Humulin I®, 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 'mealtime' 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

› **People on twice-daily pre-mix insulin**

e.g. NovoMix 30®/Humulin M3®/Humalog Mix 25®/Humalog Mix 50®

Continue mixed insulin and adjust dose (follow dose adjustment for long-acting insulin table below). Consider increasing the morning dose by 20% but this may need rapid escalation by as much as 40% each day depending on the response. There should be a low threshold for referral to the diabetes team

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 patients details and safely store

Those 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

***NATIONAL INPATIENT DIABETES COVID-19 RESPONSE GROUP:**

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Designed by: Leicester Diabetes Centre