COncise adVice on Inpatient Diabetes (COVID:Diabetes):

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

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JBDS Joint British Diabetes Societies for Inpatient care

ABCD

NATIONAL INPATIENT DIABETES COVID-19 RESPONSE GROUP*

This guidance is for use in ALL patients with COVID-19 who are treated with dexamethasone or other high doses of glucocorticosteroid therapies (subsequently to be collectively referred to as glucocorticoids) in a ward setting
This guidance may be adapted for use in Critical Care Units
In contrast to the COVID:Diabetes GUIDANCE FOR MANAGING INPATIENT HYPERGLYCAEMIA this group previously published, this guidance recommends larger insulin doses to overcome the greater insulin resistance which may be encountered in many patients treated with high doses of glucocorticoids and should ONLY be used in this context

Key Facts

- High dose glucocorticoids reduce mortality in people with COVID-19 who require ventilation or oxygen therapy
- Glucocorticoid therapy impairs glucose metabolism and is the commonest cause of life threatening inpatient Hyperosmolar Hyperglycaemic State (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
- High dose glucocorticoid regimens such as the recommended dexamethasone dose of 6 mg/d (oral or IV) used in the *recovery trial*, equivalent to 40mg of prednisolone/day will undoubtedly affect glucose metabolism
- Thus, the **triple insult** of high dose glucocorticoid therapy 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 high dose glucocorticoid regimens receive appropriate glucose surveillance and appropriate management of hyperglycaemia

GLUCOSE MONITORING

NOTE- Check HbA1c as this may 1) help differentiate stress hyperglycaemia from previously undiagnosed diabetes and 2) give an indication of the preceding glycaemic control and degree of insulin resistance

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 e.g ideally before meals, or more frequently if the glucose is outside the 6.0 -10.0 mmol/L range

MANAGING DEXAMETHASONE RELATED HYPERGLYCAEMIA

First, exclude Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic State 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 analogues (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

If after a second correction dose the glucose level remains >12 mmol/L either move to the next column or increase the algorithm by 1-3 units for each of the rows and enter the new doses in the blank dose escalation column striking out the other columns.

If after repeated correction doses the glucose level remains >12.0 mmol/L commence Variable Rate Intravenous Insulin Infusion

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	DOSE ESCALATION Enter number of units for each glucose level (see above)	←
12.0-14.9	2 units	3 units	4 units	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
15.0-16.9	2 units	3 units	5 units	units	
17.0-18.9	3 units	4 units	5 units	units	
19.0-20.9	3 units	5 units	6 units	units	
21.0-22.9	4 units	6 units	7 units	units	
23.0-24.9	4 units	7 units	8 units	units	
25.0-27.0	5 units	8 units	9 units	units	
Over 27	6 units	9 units	10 units	units	

MAINTAINING GLYCAEMIC CONTROL

Most people with hyperglycaemia will need a basal insulin to maintain glycaemic even if they respond to the correction dose. The following are suggested basal insulin regimes.

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

Where glucose has risen above 12.0 mmol/l due to glucocorticoid treatment, start NPH insulin which has an intermediate duration of action (e.g. Humulin I®, Insulatard®) - a starting total dose of 0.3 units/kg/day is conservative but experience suggests that a dose of 0.5 units/kg/day or more may be required depending on severity of illness, BMI and pre-existing diabetes control as indicated by HbA1c. 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. The choice should be based on the individual patient, for example if there is considerable postprandial hyperglycaemia with NPH and the patient is eating and drinking a premixed insulin (see examples below) may be more appropriate.

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 GLUCOCORTOID THERAPY

After glucocorticoid therapy is stopped insulin resistance and consequently insulin requirements usually fall gradually requiring a gradual reduction in insulin requirements. However in COID-19 patients a faster and a more aggressive reduction in insulin dose may be necessary. From day one, the total insulin dose may need to be reduced by as much as 50% guided by 'pre-steroid' insulin requirements. Subsequent insulin dose changes should be guided by 6 hourly glucose monitoring and input from the diabetes specialist team.

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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