COVID 19 and Diabetes

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Disclosures

- I am the lead author of the UK JBDS guidelines for the management of diabetic ketoacidosis
- I am the lead author of the JBDS guidelines on the management of the adult patient with diabetes undergoing surgery or procedures
- I am a co-author on almost all of the other JBDS national guidelines – and the Chair of JBDS
- In the last 24 months, I have received consulting fees and honoraria from Sanofi Diabetes, and Novo Nordisk

JBDS, Joint British Diabetes Societies.

Who is This Strange Man?

- I qualified in 1991
- I trained in diabetes & endocrinology and general (internal) medicine
- I worked in general practice for 2 years
- I worked in ITU/anaesthetics for a year
- I did research at the Mayo Clinic (DHEA anyone?)
- I have been in Norwich since 2004
- My current national roles are:
  - Chair of the UK Specialist Certificate Examination in Diabetes and Endocrinology and the European Board Exam in Endocrinology, Diabetes and Metabolism
  - President of the Endocrinology & Diabetes Section of the Royal Society of Medicine
  - Chair of the JBDS – IP (inpatient diabetes guidelines)
    - Peri-operative, diabetic ketoacidosis, hypoglycaemia, HHS, enteral feeding, self management, e-learning on safe use of IV insulin, renal unit, peri-partum management, steroid-induced hyperglycaemia, diabetes at the front door, the fail elderly inpatient, etc.

DHEA, dehydroepiandrosterone; HHS, hyperosmolar hyperglycaemic state; ITU, intensive therapy unit; IV, intravenous; JBDS – IP, Joint British Diabetes Societies for Inpatient Care.

COVID-19 – Risk Factors for Increased Mortality

- Increasing age
- Gender
- Ethnicity
- Underlying co-morbidities
  - Lung disease
  - Diabetes
  - Obesity
  - IHD and hypertension

Considerations – How COVID Makes Things Different

- The presentation of diabetes emergencies is worse
  - Atypical ketosis in those not know to have diabetes
  - Profound acidosis (<7.0) and ketosis (>5mmol/l)
  - Very insulin resistant – requiring hundreds of units per day
  - The cytokine storm makes them highly catabolic

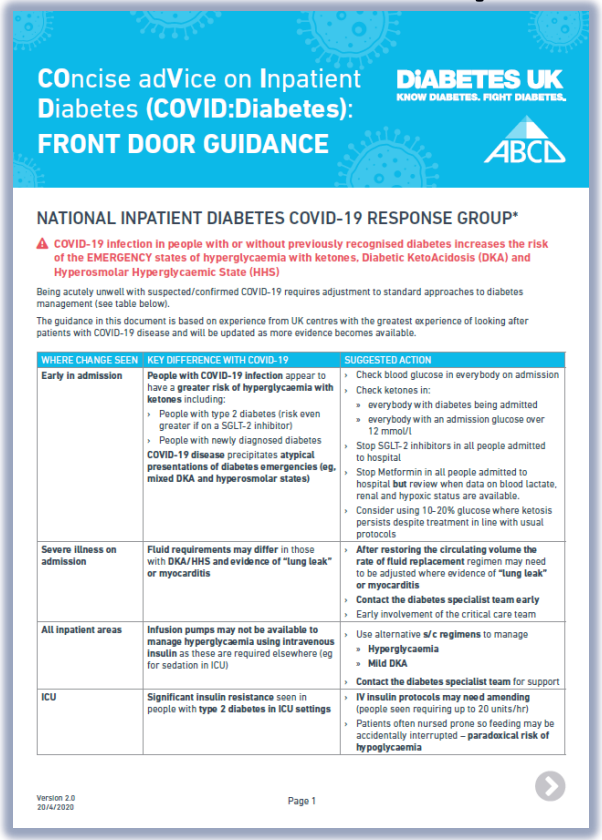

Personal View

Practical recommendations for the management of diabetes in patients with COVID-19

Introduction

Borstein SR et al Lancet Diab Endocrinol 2020 (Online 23/4/20) - https://doi.org/10.1016/S2213-8587(20)30152-2

An Example Resource – At the Front Door



COncise adVice on Inpatient Diabetes (COVID:Diabetes): FRONT DOOR GUIDANCE

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⚠ COVID-19 infection in people with or without previously recognised diabetes increases the risk of the EMERGENCY states of hyperglycaemia with ketones, Diabetic KetoAcidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS)

Being acutely unwell with suspected/confirmed COVID-19 requires adjustment to standard approaches to diabetes management (see table below).

The guidance in this document is based on experience from UK centres with the greatest experience of looking after patients with COVID-19 disease and will be updated as more evidence becomes available.

WHERE CHANGE SEEN	KEY DIFFERENCE WITH COVID-19	SUGGESTED ACTION
Early in admission	**People with COVID-19 infection** appear to have a **greater risk of hyperglycaemia with ketones** including: › People with type 2 diabetes (risk even greater if on a SGLT-2 inhibitor) › People with newly diagnosed diabetes **COVID-19 disease** precipitates **atypical presentations of diabetes emergencies (eg, mixed DKA and hyperosmolar states)**	› Check blood glucose in everybody on admission › Check ketones in: » everybody with diabetes being admitted » everybody with an admission glucose over 12 mmol/l › Stop SGLT-2 inhibitors in all people admitted to hospital › Stop Metformin in all people admitted to hospital **but** review when data on blood lactate, renal and hypoxic status are available. › Consider using 10-20% glucose where ketosis persists despite treatment in line with usual protocols
Severe illness on admission	**Fluid requirements may differ** in those with **DKA/HHS and evidence of "lung leak" or myocarditis**	› **After restoring the circulating volume the rate of fluid replacement** regimen may need to be adjusted where evidence of **"lung leak" or myocarditis** › **Contact the diabetes specialist team early** › Early involvement of the critical care team
All inpatient areas	**Infusion pumps may not be available to manage hyperglycaemia using intravenous insulin** as these are required elsewhere (eg for sedation in ICU)	› Use alternative **s/c regimens** to manage » **Hyperglycaemia** » **Mild DKA** › **Contact the diabetes specialist team** for support
ICU	**Significant insulin resistance** seen in people with **type 2 diabetes in ICU settings**	› **IV insulin protocols may need amending** (people seen requiring up to 20 units/hr) › Patients often nursed prone so feeding may be accidentally interrupted – **paradoxical risk of hypoglycaemia**

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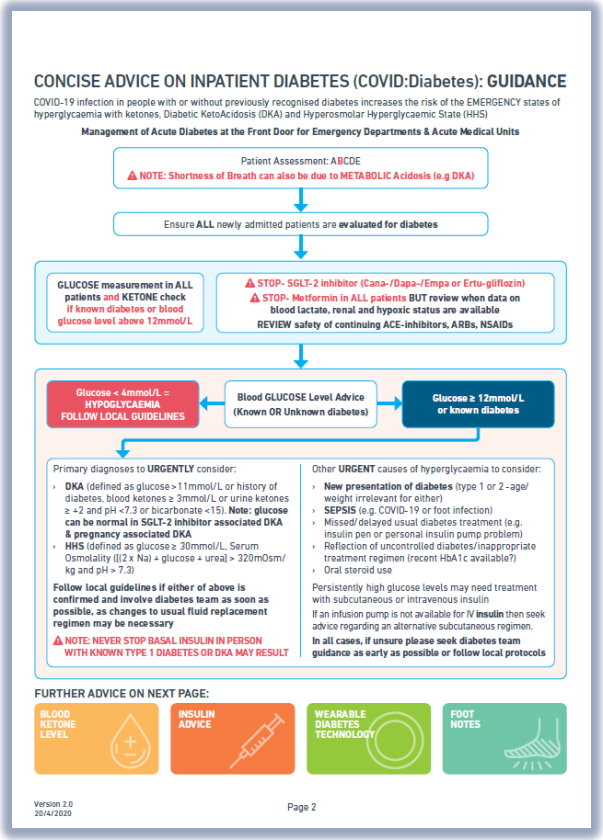

CONCISE ADVICE ON INPATIENT DIABETES (COVID:Diabetes): **GUIDANCE**

COVID-19 infection in people with or without previously recognised diabetes increases the risk of the EMERGENCY states of hyperglycaemia with ketones, Diabetic KetoAcidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS)

Management of Acute Diabetes at the Front Door for Emergency Departments & Acute Medical Units

Patient Assessment: ABCDE
⚠ NOTE: Shortness of Breath can also be due to METABOLIC Acidosis (e.g DKA)

Ensure **ALL** newly admitted patients are **evaluated for diabetes**

GLUCOSE measurement in ALL patients and KETONE check if known diabetes or blood glucose level above 12mmol/L

⚠ STOP- SGLT-2 inhibitor (Cana-/Dapa-/Empa or Ertu-gliflozin)
⚠ STOP- Metformin in ALL patients **BUT review when data on blood lactate, renal and hypoxic status are available**
REVIEW safety of continuing ACE-inhibitors, ARBs, NSAIDs

Glucose < 4mmol/L = HYPOGLYCAEMIA FOLLOW LOCAL GUIDELINES

Blood GLUCOSE Level Advice (Known OR Unknown diabetes)

Glucose ≥ 12mmol/L or known diabetes

Primary diagnoses to **URGENTLY** consider:
› **DKA** (defined as glucose >11mmol/L or history of diabetes, blood ketones ≥ 3mmol/L or urine ketones ≥ +2 and pH <7.3 or bicarbonate <15). **Note: glucose can be normal in SGLT-2 inhibitor associated DKA & pregnancy associated DKA**
› **HHS** (defined as glucose ≥ 30mmol/L, Serum Osmolality ([2 x Na) + glucose + urea] > 320mOsm/kg and pH > 7.3)

Follow local guidelines if either of above is confirmed and involve diabetes team as soon as possible, as changes to usual fluid replacement regimen may be necessary

⚠ NOTE: NEVER STOP BASAL INSULIN IN PERSON WITH KNOWN TYPE 1 DIABETES OR DKA MAY RESULT

Other **URGENT** causes of hyperglycaemia to consider:
› **New presentation of diabetes** (type 1 or 2 -age/weight irrelevant for either)
› **SEPSIS** (e.g. COVID-19 or foot infection)
› Missed/delayed usual diabetes treatment (e.g. insulin pen or personal insulin pump problem)
› Reflection of uncontrolled diabetes/inappropriate treatment regimen (recent HbA1c available?)
› Oral steroid use

Persistently high glucose levels may need treatment with subcutaneous or intravenous insulin

If an infusion pump is not available for IV **insulin** then seek advice regarding an alternative subcutaneous regimen.

In all cases, if unsure please seek diabetes team guidance as early as possible or follow local protocols

FURTHER ADVICE ON NEXT PAGE:

BLOOD KETONE LEVEL | INSULIN ADVICE | WEARABLE DIABETES TECHNOLOGY | FOOT NOTES

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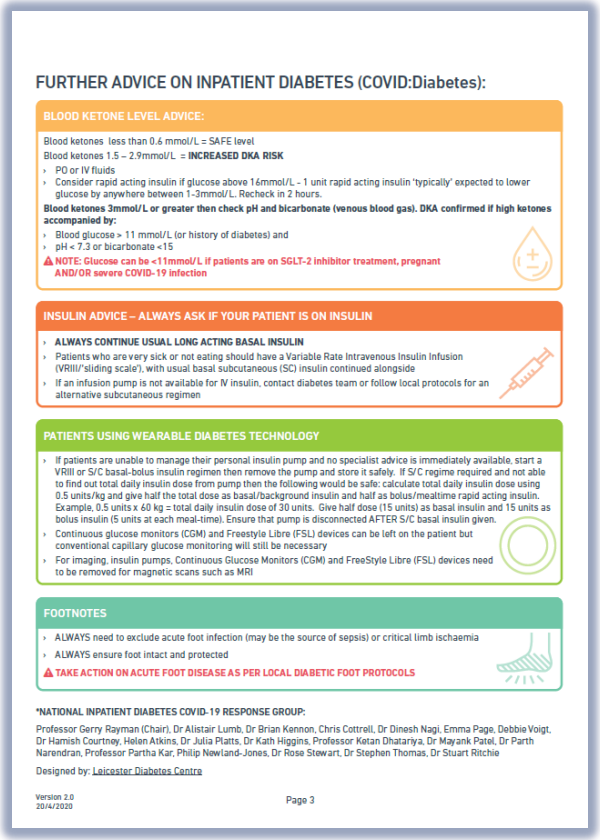

FURTHER ADVICE ON INPATIENT DIABETES (COVID:Diabetes):

BLOOD KETONE LEVEL ADVICE:

Blood ketones less than 0.6 mmol/L = SAFE level
Blood ketones 1.5 – 2.9mmol/L = **INCREASED DKA RISK**
› PO or IV fluids
› Consider rapid acting insulin if glucose above 14mmol/L - 1 unit rapid acting insulin 'typically' expected to lower glucose by anywhere between 1-3mmol/L. Recheck in 2 hours.

Blood ketones 3mmol/L or greater then check pH and bicarbonate (venous blood gas). DKA confirmed if high ketones accompanied by:
› Blood glucose > 11 mmol/L (or history of diabetes) and
› pH < 7.3 or bicarbonate <15

⚠ NOTE: Glucose can be <11mmol/L if patients are on SGLT-2 inhibitor treatment, pregnant AND/OR severe COVID-19 infection

INSULIN ADVICE – ALWAYS ASK IF YOUR PATIENT IS ON INSULIN

› **ALWAYS CONTINUE USUAL LONG ACTING BASAL INSULIN**
› Patients who are very sick or not eating should have a Variable Rate Intravenous Insulin Infusion (VRIII/'sliding scale'), with usual basal subcutaneous (SC) insulin continued alongside
› If an infusion pump is not available for IV insulin, contact diabetes team or follow local protocols for an alternative subcutaneous regimen

PATIENTS USING WEARABLE DIABETES TECHNOLOGY

› If patients are unable to manage their personal insulin pump and no specialist advice is immediately available, start a VRIII or S/C basal-bolus insulin regimen then remove the pump and store it safely. If S/C regime required and not able to find out total daily insulin dose from pump then the following would be safe: calculate total daily insulin dose using 0.5 units/kg and give half the total dose as basal/background insulin and half as bolus/mealtime rapid acting insulin. Example, 0.5 units x 60 kg = total daily insulin dose of 30 units. Give half dose (15 units) as basal insulin and 15 units as bolus insulin (5 units at each meal-time). Ensure that pump is disconnected AFTER S/C basal insulin given.
› Continuous glucose monitors (CGM) and Freestyle Libre (FSL) devices can be left on the patient but conventional capillary glucose monitoring will still be necessary
› For imaging, insulin pumps, Continuous Glucose Monitors (CGM) and FreeStyle Libre (FSL) devices need to be removed for magnetic scans such as MRI

FOOTNOTES

› ALWAYS need to exclude acute foot infection (may be the source of sepsis) or critical limb ischaemia
› ALWAYS ensure foot intact and protected

⚠ TAKE ACTION ON ACUTE FOOT DISEASE AS PER LOCAL DIABETIC FOOT PROTOCOLS

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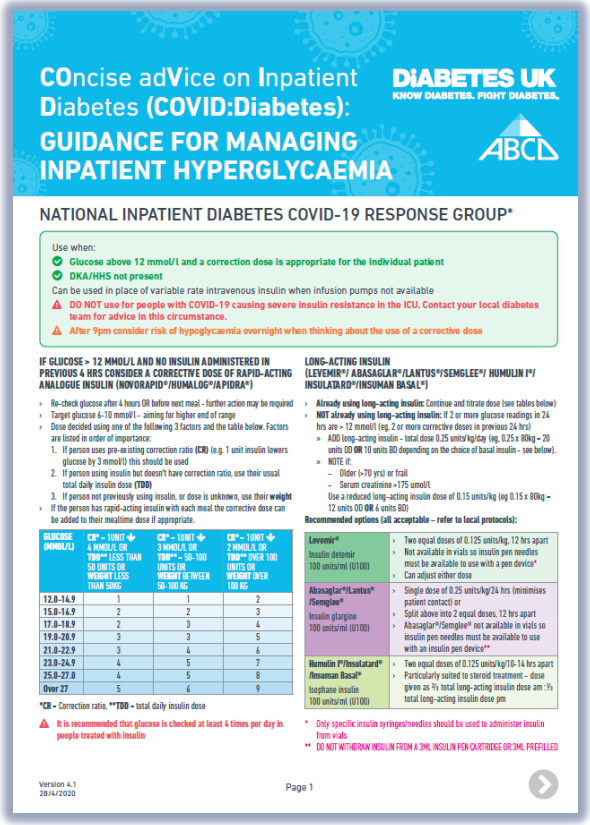
https://abcd.care/resource/concise-advice-inpatient-diabetes-during-covid19-front-door-guidance

Managing Inpatient Hyperglycaemia



COncise adVice on Inpatient Diabetes (COVID:Diabetes):

GUIDANCE FOR MANAGING INPATIENT HYPERGLYCAEMIA

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Use when:

- Glucose above 12 mmol/l and a correction dose is appropriate for the individual patient
- DKA/HHS not present

Can be used in place of variable rate intravenous insulin when infusion pumps not available

- DO NOT use for people with COVID-19 causing severe insulin resistance in the ICU. Contact your local diabetes team for advice in this circumstance.
- After 9pm consider risk of hypoglycaemia overnight when thinking about the use of a corrective dose

IF GLUCOSE > 12 MMOL/L AND NO INSULIN ADMINISTERED IN PREVIOUS 4 HRS CONSIDER A CORRECTIVE DOSE OF RAPID-ACTING ANALOGUE INSULIN (NOVORAPID®/HUMALOG®/APIDRA®)

- Re-check glucose after 4 hours OR before next meal - further action may be required
- Target glucose 6–10 mmol/L – aiming for higher end of range
- Dose decided using one of the following 3 factors and the table below. Factors are listed in order of importance:
  1. If person uses pre-existing correction ratio **(CR)** (e.g. 1 unit insulin lowers glucose by 3 mmol/l) this should be used
  2. If person using insulin but doesn't have correction ratio, use their usual total daily insulin dose **(TDD)**
  3. If person not previously using insulin, or dose is unknown, use their **weight**
- If the person has rapid-acting insulin with each meal the corrective dose can be added to their mealtime dose if appropriate.

GLUCOSE (MMOL/L)	CR* = 1UNIT ↓ 4 MMOL/L OR TDD** LESS THAN 50 UNITS OR WEIGHT LESS THAN 50KG	CR* = 1UNIT ↓ 3 MMOL/L OR TDD** = 50-100 UNITS OR WEIGHT BETWEEN 50-100 KG	CR* = 1UNIT ↓ 2 MMOL/L OR TDD** OVER 100 UNITS OR WEIGHT OVER 100 KG
12.0-14.9	1	1	2
15.0-14.9	2	2	3
17.0-18.9	2	3	4
19.0-20.9	3	3	5
21.0-22.9	3	4	6
23.0-24.9	4	5	7
25.0-27.0	4	5	8
Over 27	5	6	9

*CR – Correction ratio, **TDD – total daily insulin dose

- It is recommended that glucose is checked at least 4 times per day in people treated with insulin

LONG-ACTING INSULIN (LEVEMIR®/ ABASAGLAR®/LANTUS®/SEMGLEE®/ HUMULIN I®/ INSULATARD®/INSUMAN BASAL®)

- **Already using long-acting insulin:** Continue and titrate dose (see tables below)
- **NOT already using long-acting insulin:** If 2 or more glucose readings in 24 hrs are > 12 mmol/l (eg, 2 or more corrective doses in previous 24 hrs)
  - ADD long-acting insulin – total dose 0.25 units/kg/day (eg, 0.25 x 80kg = 20 units OD **OR** 10 units BD depending on the choice of basal insulin - see below).
  - NOTE IF:
    - Older (>70 yrs) or frail
    - Serum creatinine >175 umol/l

  Use a reduced long-acting insulin dose of 0.15 units/kg (eg 0.15 x 80kg = 12 units OD **OR** 6 units BD)

Recommended options (all acceptable – refer to local protocols):

Levemir® Insulin detemir 100 units/ml (U100)	Two equal doses of 0.125 units/kg, 12 hrs apart Not available in vials so insulin pen needles must be available to use with a pen device* Can adjust either dose
Abasaglar®/Lantus® /Semglee® Insulin glargine 100 units/ml (U100)	Single dose of 0.25 units/kg/24 hrs (minimises patient contact) or Split above into 2 equal doses, 12 hrs apart Abasaglar®/Semglee® not available in vials so insulin pen needles must be available to use with an insulin pen device**
Humulin I®/Insulatard® /Insuman Basal® Isophane insulin 100 units/ml (U100)	Two equal doses of 0.125 units/kg/10-14 hrs apart Particularly suited to steroid treatment – dose given as ⅔ total long-acting insulin dose am : ⅓ total long-acting insulin dose pm

* Only specific insulin syringes/needles should be used to administer insulin from vials

** DO NOT WITHDRAW INSULIN FROM A 3ML INSULIN PEN CARTRIDGE OR 3ML PREFILLED

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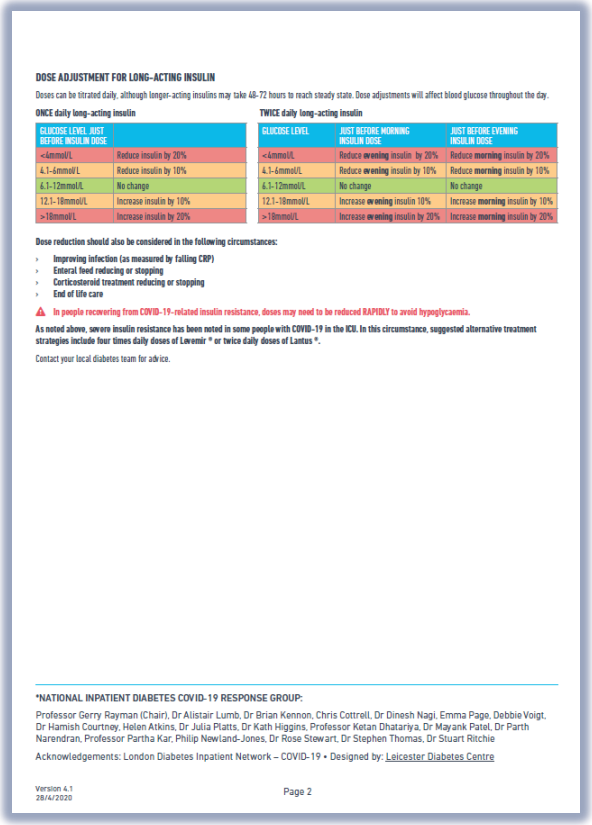

DOSE ADJUSTMENT FOR LONG-ACTING INSULIN

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 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%

Dose reduction should also be considered in the following circumstances:

- **Improving infection (as measured by falling CRP)**
- **Enteral feed reducing or stopping**
- **Corticosteroid treatment reducing or stopping**
- **End of life care**

- In people recovering from COVID-19-related insulin resistance, doses may need to be reduced RAPIDLY to avoid hypoglycaemia.

As noted above, severe insulin resistance has been noted in some people with COVID-19 in the ICU. In this circumstance, suggested alternative treatment strategies include four times daily doses of Levemir ® or twice daily doses of Lantus ®.

Contact your local diabetes team for advice.

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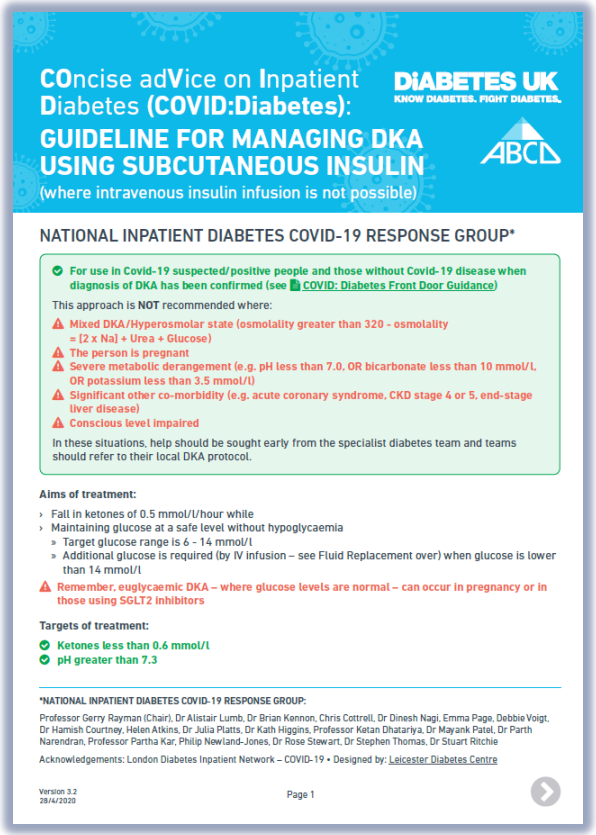
https://abcd.care/sites/abcd.care/files/resources/COvID_Hyper_v4.1.pdf

Managing DKA Without a Pump



COncise adVice on Inpatient Diabetes (COVID:Diabetes):

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GUIDELINE FOR MANAGING DKA USING SUBCUTANEOUS INSULIN

(where intravenous insulin infusion is not possible)

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✔ For use in Covid-19 suspected/positive people and those without Covid-19 disease when diagnosis of DKA has been confirmed (see COVID: Diabetes Front Door Guidance)

This approach is **NOT** recommended where:

⚠ Mixed DKA/Hyperosmolar state (osmolality greater than 320 - osmolality = [2 x Na] + Urea + Glucose)
⚠ The person is pregnant
⚠ Severe metabolic derangement (e.g. pH less than 7.0, OR bicarbonate less than 10 mmol/l, OR potassium less than 3.5 mmol/l)
⚠ Significant other co-morbidity (e.g. acute coronary syndrome, CKD stage 4 or 5, end-stage liver disease)
⚠ Conscious level impaired

In these situations, help should be sought early from the specialist diabetes team and teams should refer to their local DKA protocol.

Aims of treatment:

- Fall in ketones of 0.5 mmol/l/hour while
- Maintaining glucose at a safe level without hypoglycaemia
  - Target glucose range is 6 - 14 mmol/l
  - Additional glucose is required (by IV infusion – see Fluid Replacement over) when glucose is lower than 14 mmol/l

⚠ Remember, euglycaemic DKA – where glucose levels are normal – can occur in pregnancy or in those using SGLT2 inhibitors

Targets of treatment:

✔ Ketones less than 0.6 mmol/l
✔ pH greater than 7.3

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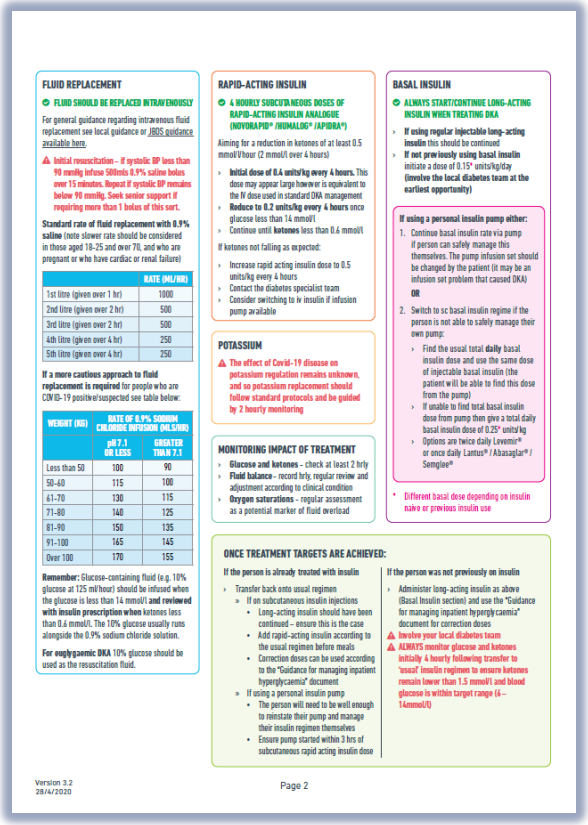

FLUID REPLACEMENT

✔ FLUID SHOULD BE REPLACED INTRAVENOUSLY

For general guidance regarding intravenous fluid replacement see local guidance or JBDS guidance available here.

⚠ Initial resuscitation – if systolic BP less than 90 mmHg infuse 500mls 0.9% saline bolus over 15 minutes. Repeat if systolic BP remains below 90 mmHg. Seek senior support if requiring more than 1 bolus of this sort.

Standard rate of fluid replacement with 0.9% saline (note slower rate should be considered in those aged 18-25 and over 70, and who are pregnant or who have cardiac or renal failure)

	RATE (ML/HR)
1st litre (given over 1 hr)	1000
2nd litre (given over 2 hr)	500
3rd litre (given over 2 hr)	500
4th litre (given over 4 hr)	250
5th litre (given over 4 hr)	250

If a more cautious approach to fluid replacement is required for people who are COVID-19 positive/suspected see table below:

WEIGHT (KG)	RATE OF 0.9% SODIUM CHLORIDE INFUSION (ML/HR)	
	pH7.1 OR LESS	GREATER THAN 7.1
Less than 50	100	90
50-60	115	100
61-70	130	115
71-80	140	125
81-90	150	135
91-100	165	145
Over 100	170	155

Remember: Glucose-containing fluid (e.g. 10% glucose at 125 ml/hour) should be infused when the glucose is less than 14 mmol/l **and reviewed with insulin prescription when** ketones less than 0.6 mmol/l. The 10% glucose usually runs alongside the 0.9% sodium chloride solution.

For euglycaemic DKA 10% glucose should be used as the resuscitation fluid.

RAPID-ACTING INSULIN

✔ 4 HOURLY SUBCUTANEOUS DOSES OF RAPID-ACTING INSULIN ANALOGUE (NOVORAPID® /HUMALOG® /APIDRA®)

Aiming for a reduction in ketones of at least 0.5 mmol/l/hour (2 mmol/l over 4 hours)

- **Initial dose of 0.4 units/kg every 4 hours.** This dose may appear large however is equivalent to the IV dose used in standard DKA management
- **Reduce to 0.2 units/kg every 4 hours** once glucose less than 14 mmol/l
- Continue until **ketones** less than 0.6 mmol/l

If ketones not falling as expected:

- Increase rapid acting insulin dose to 0.5 units/kg every 4 hours
- Contact the diabetes specialist team
- Consider switching to iv insulin if infusion pump available

POTASSIUM

⚠ The effect of Covid-19 disease on potassium regulation remains unknown, and so potassium replacement should follow standard protocols and be guided by 2 hourly monitoring

MONITORING IMPACT OF TREATMENT

- **Glucose and ketones** - check at least 2 hrly
- **Fluid balance** - record hrly, regular review and adjustment according to clinical condition
- **Oxygen saturations** - regular assessment as a potential marker of fluid overload

BASAL INSULIN

✔ ALWAYS START/CONTINUE LONG-ACTING INSULIN WHEN TREATING DKA

- **If using regular injectable long-acting insulin** this should be continued
- **If not previously using basal insulin** initiate a dose of 0.15* units/kg/day **(involve the local diabetes team at the earliest opportunity)**

If using a personal insulin pump either:

1. Continue basal insulin rate via pump if person can safely manage this themselves. The pump infusion set should be changed by the patient (it may be an infusion set problem that caused DKA)
   OR
2. Switch to sc basal insulin regime if the person is not able to safely manage their own pump:
   - Find the usual total **daily** basal insulin dose and use the same dose of injectable basal insulin (the patient will be able to find this dose from the pump)
   - If unable to find total basal insulin dose from pump then give a total daily basal insulin dose of 0.25* units/kg
   - Options are twice daily Levemir® or once daily Lantus® / Abasaglar® / Semglee®

* Different basal dose depending on insulin naive or previous insulin use

ONCE TREATMENT TARGETS ARE ACHIEVED:

If the person is already treated with insulin

- Transfer back onto usual regimen
  - If on subcutaneous insulin injections
    - Long-acting insulin should have been continued – ensure this is the case
    - Add rapid-acting insulin according to the usual regimen before meals
    - Correction doses can be used according to the "Guidance for managing inpatient hyperglycaemia" document
  - If using a personal insulin pump
    - The person will need to be well enough to reinstate their pump and manage their insulin regimen themselves
    - Ensure pump started within 3 hrs of subcutaneous rapid acting insulin dose

If the person was not previously on insulin

- Administer long-acting insulin as above (Basal Insulin section) and use the "Guidance for managing inpatient hyperglycaemia" document for correction doses

⚠ Involve your local diabetes team
⚠ ALWAYS monitor glucose and ketones initially 4 hourly following transfer to 'usual' insulin regimen to ensure ketones remain lower than 1.5 mmol/l and blood glucose is within target range (4 – 14mmol/l)

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https://abcd.care/sites/abcd.care/files/site_uploads/COvID_DKA_SC_v3.2.pdf

Considerations – How COVID Makes Things Different

- Those on ITU have additional considerations
  - NG / parenteral feeding makes glycaemic control harder
  - Frequent proning for ARDS means feed is stopped
  - Use of inotropes or glucocorticoids induced further insulin resistance
  - Fluid balance must be individualised – there is a fine balance between running them too dry and then getting AKI and flooding their ‘leaky’ ARDS lungs

Discharge Considerations

- Many people will need insulin during their admission – often for the first time
- As they become better and less catabolic, their insulin resistance improves and their insulin requirement rapidly come down
- There will need to be a way of helping them come off insulin

Useful Websites

- European
  - https://easd-elearning.org/covid-19/
- British
  - https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group
  - https://abcd.care/coronavirus
  - https://www.diabetes.org.uk/professionals/resources/coronavirus-clinical-guidance
- American
  - https://www.diabetes.org/coronavirus-covid-19

COVID 19 and Diabetes

www.norfolkdiabetes.com

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