Northern Care Alliance
NHS Foundation Trust

Management of Hyperglycaemia and Hypoglycaemia in Critical Care

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Contents

1. Overview

The purpose of this guideline is to provide a summary of care for the management of blood glucose control in adult patients in Critical Care. There is an increasing prevalence of type 2 diabetes in the population and associated with this there have been recent advances in novel antidiabetic agents that may have specific risks and benefits for critically ill patient. This document aims to provide guidance on the use of these agents in the critical care unit.

Included in this document and available as QRG's in the Policy Hub are protocols for the management of Hyperglycaemia and Hypoglycaemia and guidelines on the management of short and long-acting insulins, oral and non-insulin antidiabetic insulins for patient's admitted to critical care.

If you have any concerns about the content of this document, please contact the author or advise the Document Control Team.

2. Scope

This guideline is to be used by all doctors, advanced practitioners, pharmacists, nurses and ward managers involved in the care of adult diabetic patients admitted to the Critical Care Unit at Salford, Bury and Oldham Care Organisations.

These guidelines are for use in Critical Care only and do not aim to replace the Trust guidelines for inpatient management in each separate Care Organisation (see below).

Associated Documents

- NCAME054 – Adult Hospital Inpatient Management of Diabetes
- NCASU008 – Diabetes Management for Patients Undergoing Surgery (Section of Hospital Inpatient Management of Diabetes)
- NCACC034QRG1 – Management of Hyperglycaemia and Hypoglycaemia in Critical Care (QRG)

3. Background

1. Hyperglycaemia in critically ill patients is very common and may be associated with a pre-existing diagnosis of Diabetes Mellitus (Type 1 or 2) or may represent a stress response to critical illness.

2. Avoidance of hyperglycaemia is desirable and the ***treatment threshold above which insulin should be commenced is 10mmol/l with a target range of 6-10mmol/l.*** Treatment with exogenous insulin infusions is often required to treat hyperglycaemia. Insulin infusions are associated with hypoglycaemia and are a common cause of reported drug errors.

3. The avoidance of hypoglycaemia is of paramount importance as this has been associated with worse outcomes in critically ill patients.

4. Minimising glucose variability and increasing time in target range are important secondary targets.

5. Most recent studies have shown no benefit in mortality or length of stay in the ICU with tight versus liberal glucose control in the ICU (Gunst et al 2023) and a non-statistically significant trend towards increased mortality in trials where patients were randomised to more liberal glucose targets or where a target was used according to their baseline HbA1c. Consensus guidelines vary but most recommend a target range of between 6-10mmol/l rather than "intensive" (4.5-6.0mmol/l). This target range is different from hospital inpatient guidelines where 6-12mmol/l is considered safe. The increased nursing ratios in critical care may make tighter target ranges safe to deliver with less risk of iatrogenic hypoglycaemia.

6. The TGF-FAST trial (Gunst et al 2023) used a computerised algorithm to achieve target ranges and this was felt by the investigators to increase safety and reduce hypoglycaemia. The www.saferinsulin.org calculator is a free to use web-based calculator that is modelled on the algorithm used in the NICE-SUGAR trial (2009). This was introduced to Salford Critical Care in 2019 and has an established safety record.

7. All patients should have their HBA1c checked on admission to Intensive Care. An HbA1c of 48mmol/mol (6.5%) is recommended as the cut off point for diagnosing diabetes. A value of less than 48mmol/mol (6.5%) does not exclude diabetes.
    a. HbA1c > 60mmol/l in a patient without a known diagnosis should be referred to the Diabetes Specialist Team for ongoing management on discharge from critical care.

8. Elective surgical patients admitted to critical care with diabetes should follow the perioperative diabetes management guidelines. Any variation in guidance should be discussed and agreed as part of the Critical Care daily review.

Critical care patients have unpredictable absorption of subcutaneous medications, and this may pose a risk of both under and overdosing of insulin. Critical illness and the treatments used in Intensive Care have dynamic and unpredictable effects on insulin sensitivity and the pharmacokinetics of drugs used to treat diabetes. Review of diabetes management should form part of the structured critical care daily review and should take place for every patient who has a known diagnosis of diabetes, is on intravenous or subcutaneous insulin, a non-insulin antidiabetic drug or who has an HbA1c on admission greater than 60mmol/mol.

4. What is new in this version?

This document is a revised version of the Salford Care Organisation "Critical Care Blood Glucose Guidelines (2018)" and a new guideline for Oldham and Bury. It contains updates on:

- Revised glucose targets.
- HbA1c.
- Updated QRG's for all short & long-acting insulins and non-insulin medications.
- Guideline on the use of Fixed Rate Insulin Infusions in critical care.

5. Guideline

5.1 Hyperglycaemia

See appendix 1: Hyperglycaemia algorithm

5.1.1 Monitoring of blood glucose levels

- All patients will have an admission blood glucose checked either via an ABG / VBG sample or a laboratory serum glucose sample.

- Patients commencing enteral or parenteral feed need their BG monitoring every 4-6 hours as per trust protocol.

- A raised blood glucose > 10 mmol/l should be repeated within 2 hours and if persistently elevated the doctor / ACCP covering the unit should be informed.

- An unexpectedly high or low sample taken from an arterial line or central line port may represent dilution from the flush line or contamination with glucose and should be checked with capillary POC sample. The contents of the flush solution must be checked to confirm that it contains no glucose. POC capillary glucose is the least accurate method (particularly in the critically ill patient) and an unexpectedly abnormal sample should be checked against an ABG/VBG or laboratory serum glucose sample.

- If a Variable Rate Insulin Infusion (VRII) is commenced, then blood glucose should be checked hourly, ideally via ABG / VBG. POC Capillary Sampling is acceptable if a patient's glucose control has been stable over the previous 24 hours and no arterial or central line access is available for monitoring. There may be considerable difference between POC analysis and gas analyser results (up to 2mmol/l) so once one method is used it is preferable to continue with this. Unexpected or grossly abnormal results must be checked with another device or with an ABG/VBG.

- If a VRII is being stopped or is no longer required blood glucose should be monitored hourly for at least 4 hours after discontinuing. This is particularly relevant when stopping for procedures or scans.

5.1.2 Target blood glucose range

- A VRII should be commenced if a patient's blood glucose is confirmed to be > 10mmol/l on 2 separate readings taken 1-2 hours apart.

- Target range for glucose control in critical care is 6-10mmol/l. This differs from ward areas where a range of 6-12mmol/l is standard. The best evidence in critical care

supports a target less than 10mmol/l and with a higher staffing ratio compared to ward level care, this can be achieved safely.

- Pending further evidence to support individualised treatment thresholds and target ranges according to preadmission glycaemic control, all patients will be initiated on the above protocol.

- Admission diabetic status and HbA1c should be documented to facilitate management post critical care and to aid decision making in individual cases where large doses of exogenous insulin are required.

5.2 Commencing a Variable Rate Insulin Infusion (VRII)

- Insulin Actrapid 50units in Sodium Chloride 0.9% 50ml should be used via a dedicated peripheral cannula or central lumen that has been confirmed to be patent and can be easily aspirated and flushed. It should be prescribed on the electronic prescription.
- A dynamic VRII is available at www.saferinsulin.org (only to be used by staff who are trained and with Consultant approval).
    - This calculator should be used as first line for all patients admitted to ICU and whilst critically ill.
    - The details of blood glucose, current insulin rate and new insulin rate should be recorded on the Critical Care observation chart.
    - The calculator reference code should be copied and pasted into the patient's electronic prescription chart against the intravenous insulin prescription.
    - During outages of the electronic prescription, it is reasonable to solely record glucose and insulin rate on the paper chart. The governance code can be omitted until electronic access restored.
    - Should the calculator be unavailable for any reason, a paper based VRII can be used. This VRII is dependent on the site and can be access via Hospital inpatient guidelines.
- As a patient's condition improves and their Level of Care approaches ward-based care, it is expected to transition to a ward based VRII as per Trust guidelines. If there is an ongoing need for intravenous insulin to control blood glucose, this should be discussed with the Diabetes Specialist Nurse prior to discharge.

Insulin preparations should be replaced every 24 hours to minimise the loss of potency.

5.3 Commencing a Fixed Rate Insulin Infusion (FRII)

- A Fixed Rate Insulin Infusion (FRII) is indicated for the treatment of Diabetic Ketoacidosis. The potential advantages of a FRII over a Variable Rate Insulin Infusion (VRII) are that the insulin rate remains high to suppress ketogenesis, even after the blood glucose starts to fall. This is of particular use in euglycaemic DKA secondary to SGLT-2 use, alcoholic or starvation ketoacidosis.
- At the time of writing an NCA wide policy is submitted for the inpatient management of diabetes emergencies which covers DKA. There is variability in guidelines and protocols according to each Care Organisation. This section exists to provide guidance for the management of an FRII in Salford and Bury Critical Care Units only. For patients admitted to Oldham Critical Unit follow the OCO DKA management pathway.

- **Diabetic ketoacidosis is most often managed outside of the Critical Care Unit and treatment should adhere to local site DKA guidelines. The decision to use a FRII or**

VRII should be according to local guidelines and at the discretion of the team responsible for the patient.

- Should a patient require referral to Critical Care for any indication as listed in the DKA pathway, this should be discussed with the ICU Registrar. A FRII may be started outside of ICU pending admission to the unit according to these guidelines. Whilst severity of DKA is a consideration for admission to critical care and a FRII may be considered according to this, the initiation of a FRII is not a sole indication for admission to critical care.

- It is essential that all patients started on a FRII should have their **blood glucose monitored at least every hour**. Intravenous insulin is a high-risk medication, and its use should be flagged at every nursing handover.

- Ensure patient's usual long-acting insulins are prescribed and given at their normal times.

- Patients admitted with DKA to critical care are likely to have significant fluid and electrolyte imbalances. IV fluid resuscitation should be led by a senior intensive care doctor/ACCP and should incorporate bedside clinical assessment, Focussed Intensive Care Echocardiography and consideration of invasive cardiac output monitoring. The recommended rates of IV fluid and electrolytes in the DKA pathways are to be considered a first line of treatment but variance is expected and should be documented in the management plan. Cerebral oedema is a serious complication that may arise following resuscitation of DKA, and fluid should be administered with caution to minimise this risk (see suggested fluid prescription in chart below).

- Monitoring of capillary blood glucose, ketones and blood gases should be according to the Trust DKA protocol as a minimum. More regular invasive monitoring may be necessary in patients who are critically ill or who develop DKA in addition to other critical illness.

- If a central line is indicated for severe electrolyte disturbance or for other medications, potassium and other electrolytes can be prescribed according to usual practice. Choice of replacement fluid can therefore be altered accordingly.

- **Emergency hypoglycaemia medication should be prescribed PRN at the time of the prescription** (see section 5.4 Hypoglycaemia). This should be appropriate to the patient's IV access (central vs peripheral) and enteral route and should be updated regularly.

Fixed Rate Insulin Infusion on Critical Care

- Infusion to be prescribed on patient's EPR or Critical Care infusion chart as "Insulin Actrapid 50units in Sodium Chloride 0.9% 50ml"
- Prescribe rate as "mls/hr" according to actual body weight below from chart below and whether patient is on a 0.05 or 0.1 unit/kg/hour infusion (depending on rate of response and blood glucose) Consider increasing by 0.1unit/kg/hr if
  - blood ketones not falling by 0.5mmol/l/hr or
  - Bicarbonate not rising by 3mmol/l or
  - CBG not falling by 3mmol/l/hr
- Consider reducing rate from 0.1 to 0.05 unit/kg/hr if blood glucose < 14mmol/l

IV Fluid – to be guided by medical team with regular assessment of cardiac output and volume status – suggested starting points

- 1litre 0.9% sodium chloride/CSL/plasmalyte over 1 hour
- 1litre 0.9% sodium chloride /CSL/plasmalyte over 2 hours***
- 1litre 0.9% sodium chloride /CSL/plasmalyte over 2 hours***
- 1litre 0.9% sodium chloride /CSL/plasmalyte over 4 hours***

***** Use added Potassium chloride to maintain normal serum potassium**

K+ > 5.0 no KCl
K+ 3.6-5.0mmo/L add 20mmol/L KCl
K+ < 3.5mmol/L add 40mmol/L KCl

- **When blood glucose falls below 14mmol/l commence 10% glucose infusion at 125ml/hr**

Monitoring

Blood glucose and capillary ketones – hourly
VBG or ABG – 2 hourly

Actual body weight (Kg)	Insulin rate (ml/hr) 0.1units/kg/hr when glucose > 14mmol/l	Insulin rate (ml/hr) 0.05units/kg/hr when glucose < 14mmol/l
40-49	4	2
50-59	5	2.5
60-69	6	3
70-79	7	3.5
80-89	8	4
90-99	9	4.5
100-109	10	5
110-119	11	5.5
120-130	12	6
130-139	13	6.5
140-150	14	7
>150	15	7.5

Hyperglycaemia Protocol in Critical Care

(Diabetic Ketoacidosis /Hyperosmotic emergencies—use Trust Protocols)

ESTABLISH DIAGNOSIS

All admissions should have HbA1c and laboratory or ABG/VBG glucose checked
Glucose should be checked every 6 hours in the critically ill patient, daily when more stable

Known diagnosis of diabetes

Review and prescribe usual medications as appropriate (see QRG)

HbA1c >60mmol/mol
Poor control, at greater risk of complications from IV insulin such as hypoglycaemia

Request non urgent DSN review

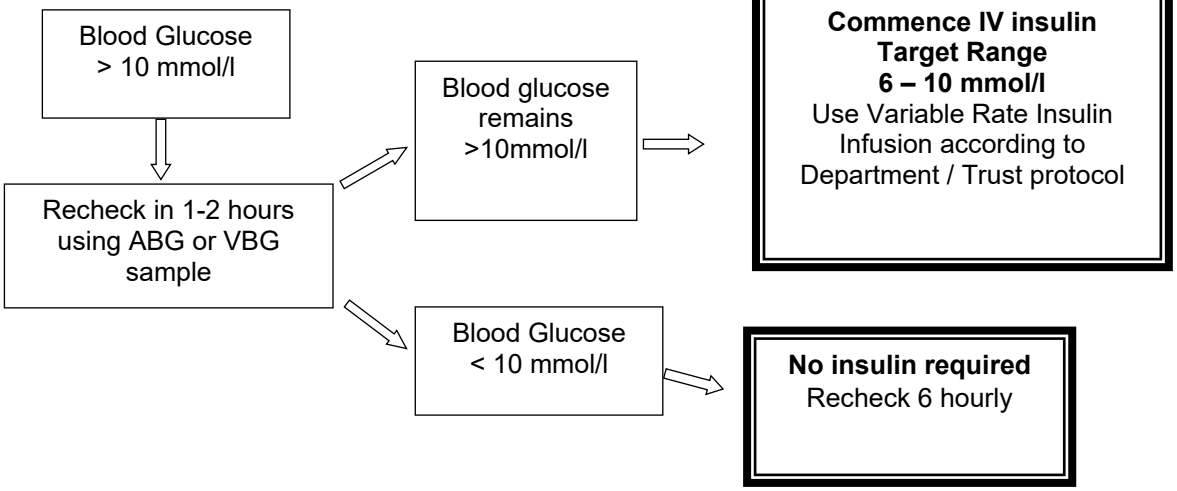
No previous diagnosis of diabetes

HbA1c > 48mmol/mol
New diagnosis of diabetes
(Type 1 / Type 2 / gestational)
Request DSN review

HbA1c < 48mmol/mol
Critical illness (Stress) Hyperglycaemia
Steroid Induced Hyperglycaemia
(Does not exclude Diabetes)

Accuracy of Glucose Measurements
Laboratory sample = ABG or VBG on gas analyser > Arterial blood on POC >>Capillary (finger prick) POC**
**Accuracy in capillary samples is worse at extremes of measurement in critically ill patients.
(any unexpected low or high sample should be double checked with another sample from a different source)

COMMENCE TREATMENT



DAILY REVIEW

Hypoglycaemia	Review episodes, assess and document risk factors and adjust medication and nutrition to minimise repeat episodes
IV Insulin	Calculate total insulin requirements last 24 hours. Consider adding other medication if diabetic (metformin/long-acting insulin) > 48 units in 24 hours = high risk
Glucose Checks	Is glucose being checked frequently enough? Ensure bead head sign and discuss barriers to sampling and high risk medications at handovers
HbA1c	Was HbA1c checked on admission? Discuss and document diabetes diagnosis in notes. Refer to DSN if > 60mmol/mol
Long-acting Insulin	Review daily (see separate QRG). Consider titration according to daily insulin requirement. Check availability of long-acting with nurse/pharmacist.
Oral & other diabetes medications	Can usual medications be restarted? Review daily (see separate QRG).

5.4 Long-acting Insulin, Oral and other non-insulin Antidiabetic Agents

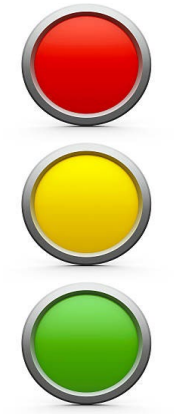
Early review is recommended of patients' usual insulin and oral / non-insulin antidiabetic agents. Continuation of a person with diabetes' normal medications may decrease the need for intravenous insulin and minimise glycaemic variability. These guidelines highlight potential risks with continuation or restarting of these medications and can be implemented by the critical care team.

The initiation of *new* diabetes medications should be discussed with the Diabetes Specialist Team and Critical Care Pharmacist. Metformin and long-acting insulin can be initiated by a senior critical care clinician according to the guidelines below, please discuss with the pharmacist on the ICU ward round.

SGLT-2 INHBITORS (GLIFLOZINS) / SULPHONYLUREAS / MEGLITINIDES/ THIAZOLIDINEDIONE

GLP-1 AGONISTS
DDP-4 ANTAGONISTS

METFORMIN
BASAL INSULINS



5.4.1 Basal / Long-acting & Intermediate acting Insulin

- Patients with Type 1 Diabetes should continue their normal (100%) long-acting insulin dose ensuring they are receiving enteral feed, parental nutrition or a glucose containing fluid.
- If a patient with Type 1 diabetes is unable to confirm their normal insulin or dose then prescribe Levemir 6 units bd.

- Patients with an insulin pump should in most cases have their pump removed on admission and switched to a VRII. The exception to this would be a patient who is able to adequately manage their own insulin pump appropriately. If disconnected a basal insulin will need to be prescribed in its absence, the Diabetes Team should be consulted as soon as possible. See Adult Hospital Inpatient Management of Diabetes Guidelines.

- Absorption via the subcutaneous route is reduced in states of peripheral vasoconstriction and shock. Studies have shown that low molecular weight heparin absorption is impaired in patients on high dose vasopressors. Insulin absorption has been shown to be impaired by tissue oedema. **Caution should be taken using basal / long or immediate acting insulins in patients who are on high dose vasopressors, are shocked or who have widespread subcutaneous oedema**.

- Patients with Type 2 Diabetes should aim to have their basal/long or immediate acting insulin prescribed at 75% of their normal prescription and dose once they have been established on enteral or PN feed.

- If there is any doubt about patient's normal dose or compliance, then consider starting a long-acting insulin (see Appendix) 10units subcutaneously once daily as a starting dose, and/or discuss with the diabetes team.

- Patients with an established diagnosis of diabetes (or those not previously diagnosed who have an HbA1c > 48mmol/l) who have been on a VRII for more than 24-48 hours and have been established on enteral or PN feed can be considered for basal subcutaneous insulin. **This should be prescribed as Humilin I (or Lantus if not available) at 75% of the total daily insulin requirement (of the previous 24 hours) split into two doses bd**. This should reduce the dose of intravenous insulin required. A DSN referral should be completed for all patients starting basal insulin when on ICU. First line

- Increases of basal insulin doses should be gradual (ideally every 48-72 hours) and not by more than 20% of the current dose. This may be modified after review by the Diabetes Specialist Nurse (DSN) or medical team depending upon local practice.

- Long-acting insulins should be administered to the abdomen, legs, buttocks, or upper arms away from sites of scarring, lipo-hypertrophy (hard lumps) and sites of infection. If there is widespread oedema the injection should be to the upper arms.

- Long-acting insulin should not be started for patients in critical care in whom HbA1c < 48mmol/l and are non-diabetic. Hyperglycaemia is likely to be transient and resolve when critical illness resolves. Please consult the diabetes team if any queries on this point.

- Long-acting insulin may be started short term for patients in critical care who are felt to have hyperglycaemia secondary to steroid use, continuation of basal insulin should be reviewed when steroids cease. Their use should be guided by the DSN. This should be highlighted in the Critical Care Transfer/Discharge summary.

- Insulin requirements may fall rapidly on resolution of critical illness and should prompt review of basal insulin dose if blood glucose is persistently below the target. The target range for patients using subcutaneous long-acting insulin on ward level care is generally 6-12mmol/l. If a patient on critical care is stepping down from intravenous insulin and is being managed solely on subcutaneous insulin, this variation in target range should be documented in the diabetes management plan.

- Patients should continue their usual brand/type of long-acting insulin where possible. In situations where these insulins are not immediately available due to stock issues and all efforts have been made to obtain their usual prescribed medication, it is acceptable to substitute another insulin from the list below, ideally of the same "type". Omitting a prescribed long-acting insulin should be avoided and delays to administration put patients at risk of DKA, hypoglycaemia and increased glucose variability. **If the patient's normal insulin is not available to be given within 1 hour of the prescribed time, use the recommended long-acting insulin below and ensure given promptly. It is not acceptable to delay the administration because, for example the insulin has not arrived from pharmacy in time.**

Patient normally takes:		First line (if immediately available)	Second line (if not immediately available)
Basal / long-acting insulins			
Insulin type	**Brand name**		
Insulin Glargine	Lantus	Usual insulin	Lantus (same dose) at 10pm
Insulin Glargine	Toujeo	Usual insulin	Lantus (same dose) at 10pm
Insulin Glargine	Abasalgar	Usual insulin	Lantus (same dose) at 10pm
Insulin Detemir	Levemir	Usual insulin	Lantus (same dose)
Insulin Degludec	Tresiba	Usual insulin	Levemir (same dose split bd)
Isophane Insulin	Humilin I	Usual insulin	Insulatard (same dose usual time)
Isophane Insulin	Insulatard	Usual insulin	Humilin I (same dose usual time)
Rapid / short-acting insulins			
Insulin Aspart	Fiasp	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Aspart	Novorapid	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Aspart	Trurapi	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Glulusine	Apidra	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Lispro	Humalog	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Lispro	Sanofi	Usual insulin	Novorapid or Actrapid (same dose)
Insulin Lispro	Lyumjev	Usual insulin	Novorapid or Actrapid (same dose)

- **Mixed / Combination insulins** (e.g., Humulin M3)
  These preparations contain both short or rapid acting insulin plus an intermediate acting insulin in a fixed ratio (Humulin M3 = 30% short-acting, 70% long-acting)
  The unpredictable tissue absorption and switch from normal diet means that these are of increased risk in critically ill patients.
  If a patient normally takes a mixed insulin and is admitted to ICU, in general their mixed insulin should be converted to a long-acting insulin to avoid boluses of short acting insulin.

To convert mixed insulin to long acting insulin only use 75% of the total dose of mixed insulin usually taken over 24 hours into a twice daily dose of a long-acting insulin.

For example: patient normally takes Humulin M3 24 units morning and 16 units evening.

Prescribe: Long-acting insulin @ 75% of total daily dose divided 12 hourly

= [(24+16) x 0.75] / 2

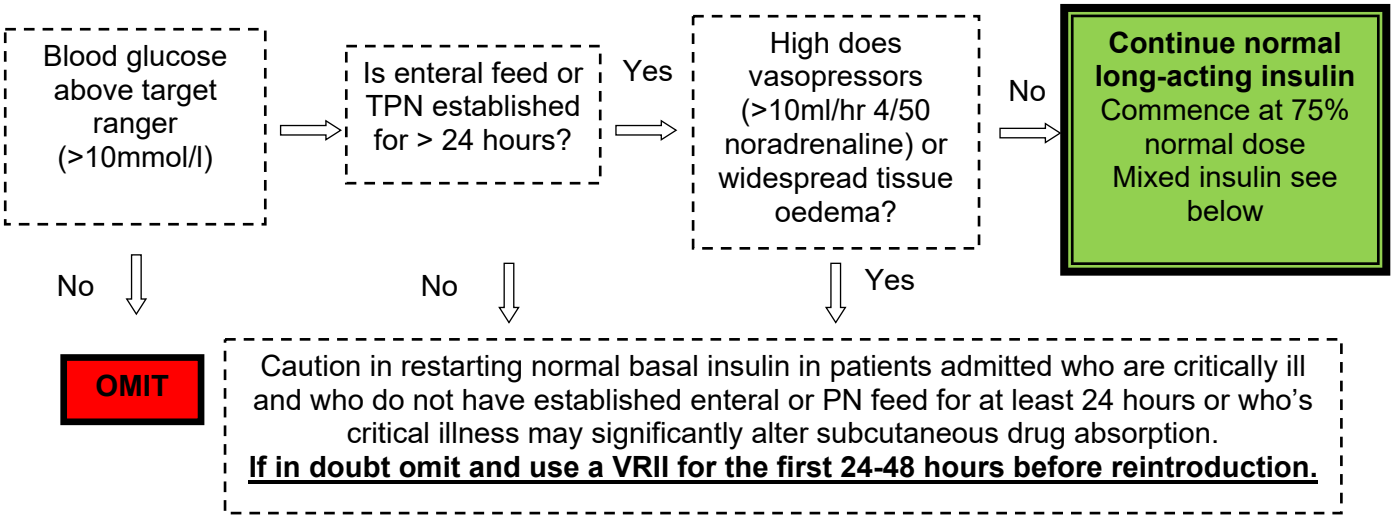
= 15 units of Levemir 12 hourly (bd)

Long-acting (basal) Insulins
Long acting insulins are used in persons with diabetes to replace or in addition to background insulin release by the pancreas. They be given once or twice daily via subcutaneous injection.
Examples: Lantus, Toujeo & Abasalgar (insulin glargine), Levemir (insulin detemir), Tresiba (insulin degludec), Insulatard / Humilin I (Isophane insulin)

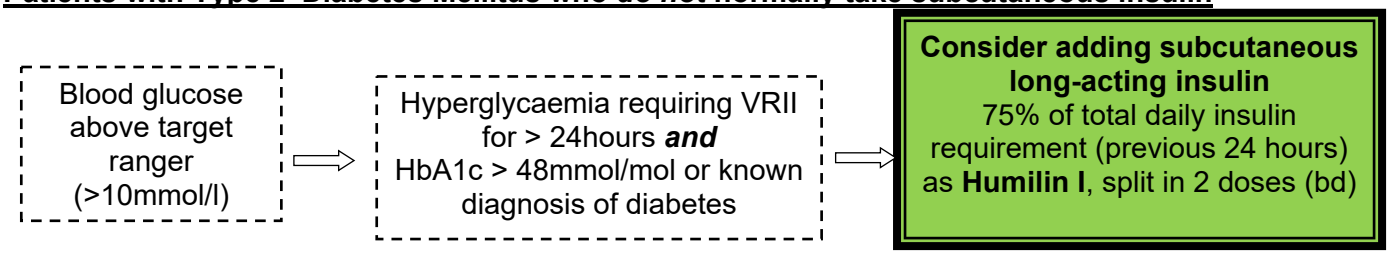
Patients with Type 1 Diabetes Mellitus who normally take subcutaneous insulin

Do not omit long-acting insulin in patients with Type 1 Diabetes
Prescribe patient's usual dose and ensure appropriate background nutrition.

Patients with Type 2 Diabetes Mellitus who normally take subcutaneous



Patients with Type 2 Diabetes Mellitus who *do not* normally take subcutaneous insulin



Long-acting insulin should not be started for patients in critical care in whom HbA1c < 48mmol/l and are non-diabetic. Hyperglycaemia is likely to be transient and resolve when critical illness resolves.

Blood glucose target range in critical care is 6.0 –10.0mmol/l. However on subcutaneous insulin and when critical illness is resolving, this target range may be increased to 6.0 –12.0mmol/l in line with ward guidelines. This change should be clearly documented in the Diabetes Management Plan.
Subcutaneous absorption is affected by vasopressors, oedema, shock, hypothermia, pyrexia. Long-acting insulin should be administered subcutaneously in tissue least affected by oedema and localised scarring or lipohypertrophy. The area with best absorption is assumed to be the abdomen but in cases where marked dependent oedema occurs, the upper arm may be preferable.
Dose adjustments should be 20% at most every 48-72 hours (seek advice from Diabetes Specialist Nurse).
Basal Insulin should be started with caution in Steroid Induced Hyperglycaemia, particularly in short courses of steroids. Contact Diabetes team if starting for medium or long term courses and before discharge from Critical Care.
Mixed insulin—prescribe 75% of total 24-hour dose as long-acting insulin (Levemir) split into 2 doses 12 hourly.

5.5 Metformin

- Metformin may be associated with lactic acidosis in critically ill patients with shock, hepatic impairment, or acute and chronic renal failure. It is excreted unchanged by the kidney and cannot be metabolised, therefore will accumulate rapidly in acute kidney injury.

- Metformin should be suspended in patients with:

    - No enteral route / surgical contraindication to enteral medications
    - Shock requiring > 10ml/hr (4mg/50ml) noradrenaline or equivalent
    - Acute or chronic liver failure
    - Acute kidney injury (AKI) Stage 2 or 3 (increase serum creatinine >200%, urine output < 0.5ml/kg/hr for >12hours or on renal replacement therapy)
    - Lactic Acidosis (Lactate >2mmol/L)

- Metformin may be associated with improved survival in patients presenting to critical care who have Type 2 diabetes and are already taking metformin or have sepsis. It may reduce the need for intravenous insulin and therefore minimise glycaemic variability, so continuation is to be considered in the absence of risk factors above.

- Metformin dose may need adjusting according to eGFR in chronic renal failure or stable AKI or on CVVHF (seek Pharmacy advice).

- In patients admitted with a high HbA1c (>48mmol/l) who are requiring intravenous insulin to control hyperglycaemia, consider starting metformin once enteral feed is established if none of the above contraindications exist. The recommended starting dose is 500mg bd but this can be increased to 500mg tds with no gastrointestinal side effects.

Metformin
Biguanides. An oral medication that decreases hepatic glucose production and increases peripheral glucose uptake without risk of hypoglycaemia.

Patients with Type 2 Diabetes Mellitus who normally take metformin

- No enteral route / surgical contraindication to enteral medications
- Shock requiring > 10ml/hr (4mg/50ml) noradrenaline or equivalent
- Acute or chronic liver failure
- Acute kidney injury (AKI) Stage 2 or 3 (increase serum creatinine >200%, urine output < 0.5ml/kg/hr for >12hours or on renal replacement therapy)
- Lactic Acidosis (Lactate >2mmol/L)

No ⇨ **Continue metformin** Liquid preparation for NG use (not modified release)

⇨ Yes **OMIT**

Patients with Type 2 Diabetes Mellitus who do not normally take metformin OR new diagnosis of diabetes with blood glucose > 10mmol/l)

Hyperglycaemia (>10mmol/l) requiring IV insulin in last 24 hours ⇨ Type 2 Diabetes Mellitus diagnosis OR HbA1c > 48mmol/mol on this admission ⇨ Check contraindications above ⇨ **Consider starting metformin 500mg bd**

May be associated with a lactic acidosis in patients with shock, renal impairment or in liver injury, omit in these circumstances.

Unlikely to be a cause of hypoglycaemia. May reduce the need for intravenous insulin and therefore decrease glucose variability.

Early reintroduction may be beneficial in critically ill patients already taking metformin. If enteral feed is established and no surgical contraindications consider restarting early

Monitor lactate—if rising above 2mmol/l omit metformin.
Metformin is excreted unchanged in the kidney and can accumulate rapidly in Acute Kidney Injury, it's use in critical care should be reviewed daily.

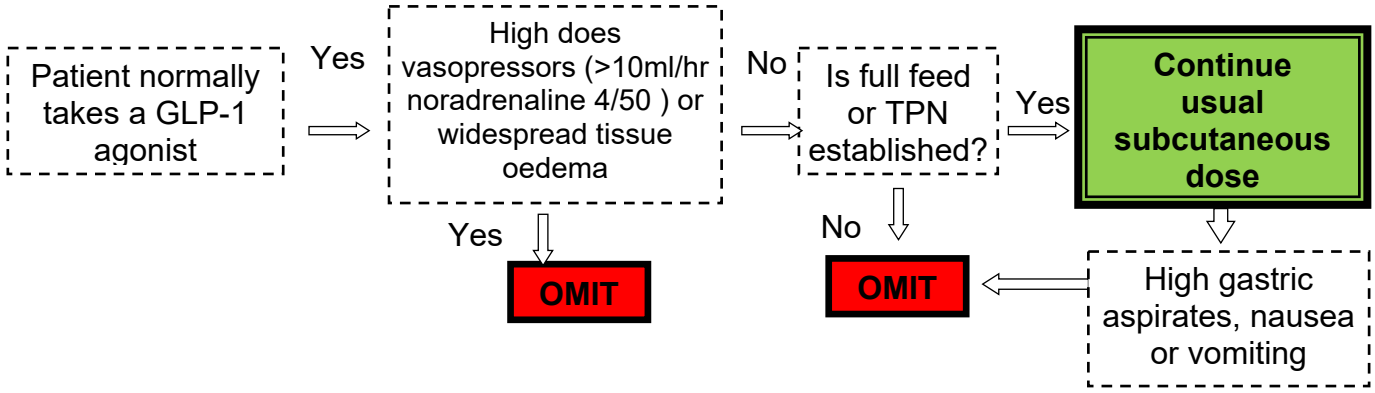
5.6 Glucose-like-peptide (GLP) 1 Analogues

- Liraglutide, Dulaglutide and Semaglutide are subcutaneously administered medications and absorption may be unpredictable in critically ill patients. They should be suspended in patients admitted to critical care with evidence of shock requiring vasopressors (greater than 10ml/hr of 4mg/50ml noradrenaline).

- The GLP1 analogues act by increasing incretin levels which reduce gastric emptying. A common side effect is nausea and vomiting. If there are concerns regarding high gastric aspirates, paralytic ileus or vomiting then these agents should be suspended.

GLP-1 agonists have been demonstrated to be an effective agent in controlling blood glucose in critically ill patients at high doses, but their use at high doses was limited by gastrointestinal side effects. In the absence of high gastric aspirates or nausea these agents can be safely continued in patients who are already using them.

<u>Glucagon-like peptide-1 (GLP-1) agonists:</u> Exenatide/Liraglutide/Semaglutide
Subcutaneous injection. Incretin mimetic, blocks glucagon release, increases insulin release to glucose and slow gastric emptying

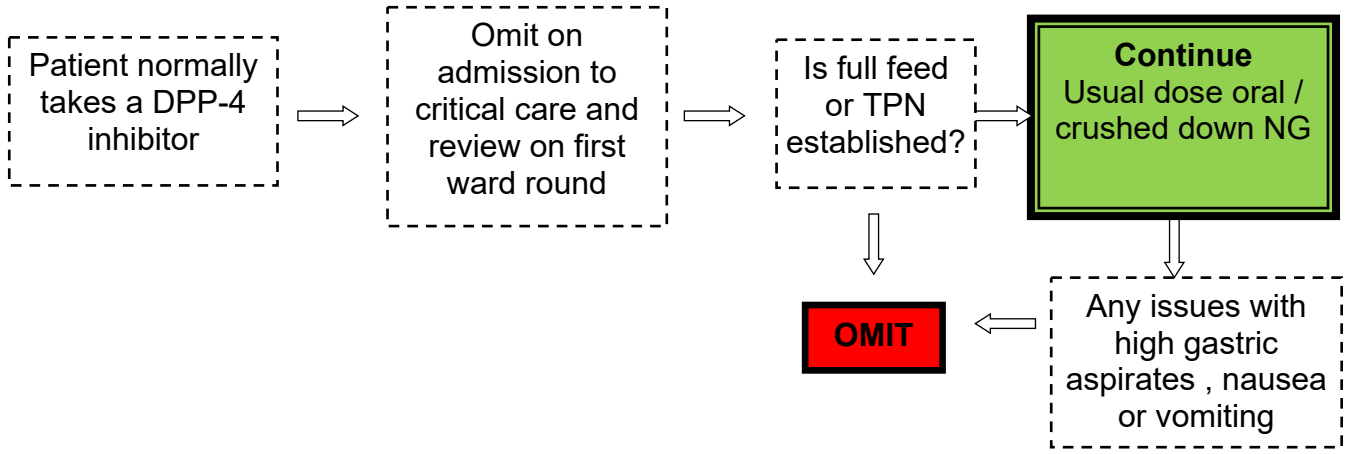


Exanatide,Lirgalutide and other GLP-1 agonists cause delayed gastric emptying (and therefore reduce postprandial hyperglycaemia). This may cause problems with absorbing NG feed. Should be stopped in patients with high GI aspirates.
The risk of hypoglycaemia is low. GLP-1 agonists have been demonstrated to be an effective agent in controlling blood glucose in critically ill patients at high doses, but their use at high doses was limited by gastrointestinal side effects. In the absence of high gastric aspirates or nausea these agents can be safely continued in patients who are already using them .
Continuing usual diabetes medications reduces the need for IV insulin and improves glycaemic variability

5.6 Dipeptidyl peptidase-4 (DPP-4) inhibitors

- Sitagliptin and Linagliptin are oral agents that stimulate incretin release and supress glucagon. They have a similar mechanism of action to the GLP-1 analogues and could therefore be reintroduced to patients who are already prescribed these medications once the enteral route has been established. However, they should be discontinued in high gastric aspirates, nausea or vomiting. Check with pharmacist if tablets can be crushed for NG administration.

<u>Dipeptidyl peptidase-4 (DPP-4) inhibitors:</u> Sitagliptin / Linagliptin
Oral medication with a similar mechanism to the GLP-1 agonists. Increase incretin levels therefore suppress glucagon release, increases insulin release to glucose and slow gastric emptying.



May be associated with GI disturbance, nausea, vomiting
Rare reports of pancreatitis

Less risk of hypoglycaemia than other antidiabetic agents

5.7 Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- SGLT-2 inhibitors reduce the renal reabsorption of glucose by inhibiting the SGLT-2 transporter in the loop of Henle. They lower the threshold at which glucose is excreted in the urine and result in a loss of glucose (as well as water). They have been shown to improve mortality in patients with Type 2 diabetes mellitus and those with congestive cardiac failure and their use in the community is increasing. They pose significant risks in patients admitted with critical illness and must be discontinued on admission.

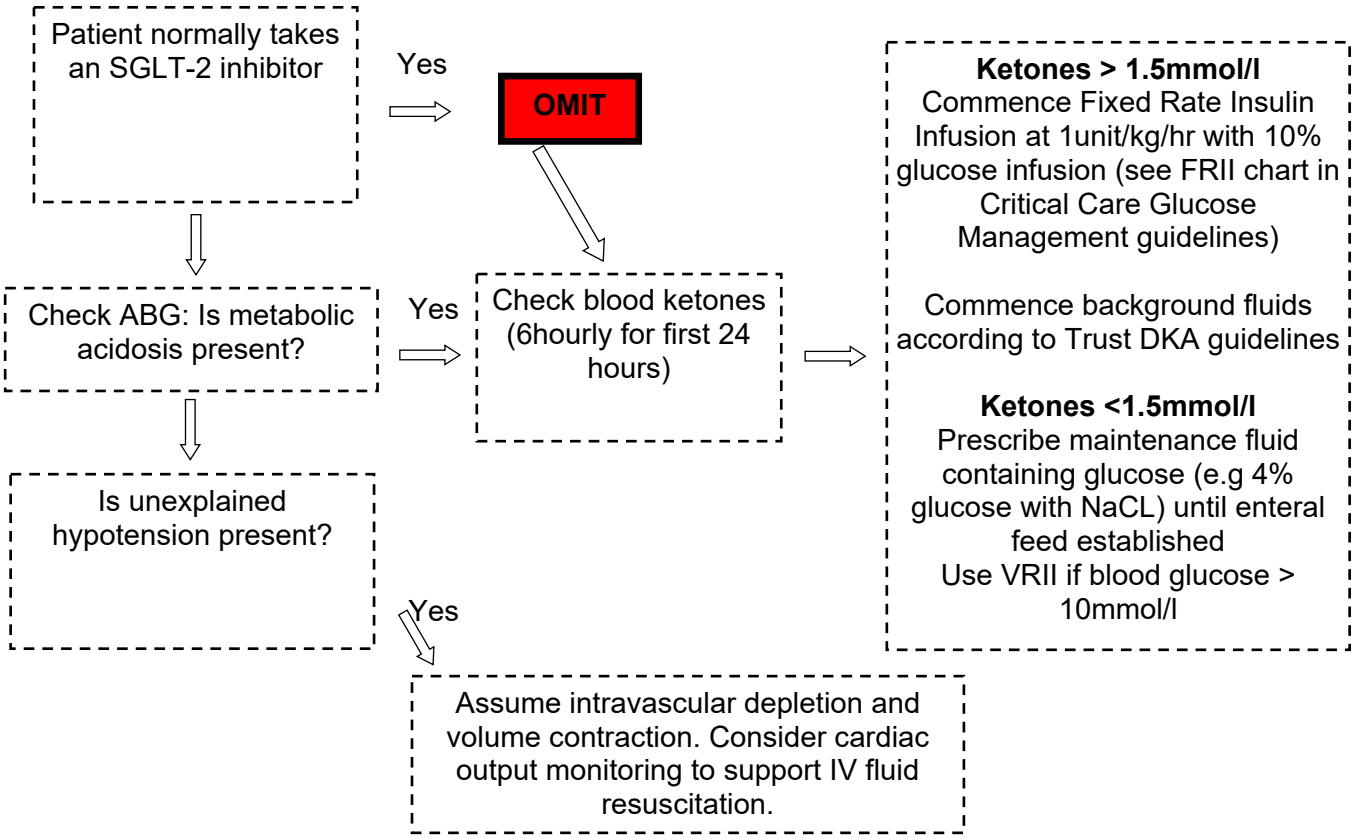
- They are associated with a euglycemic ketoacidosis that may exist for several days after discontinuation of treatment. This is a particular risk to critically ill patients **and those patients that have a sudden reduction in calorie intake**. Unexplained acidosis in a patient admitted who has been taking a SGLT-2 inhibitor should prompt investigation for ketoacidosis even in the context of normal glucose levels.

- **Any patient taking an SGLT-2 inhibitor should have their capillary ketones measured on arrival to critical care and every 6 hours for the next 24 hours.** After this period any unexplained raised anion gap acidosis should prompt repeat ketone measurement. If capillary blood ketones are > 1.5mmol/l and metabolic acidosis is present, then commence a Fixed Rate Insulin Infusion (start at 1unit/kg/hr) alongside a 10% glucose infusion. If blood glucose is persistently below 10mmol/l despite a 10% glucose infusion, then reduce FRII to 0.05units/kg/hour. If metabolic acidosis fails to start correcting within 4-6 hours, then increase by 1 unit/kg/hr.

- Patient's taking SGLT-2 inhibitors may have a contracted intravenous volume resulting from the osmotic diuresis that they induce. When presenting with critical illness this can result in a profoundly dehydrated state and fluid and electrolyte resuscitation should be guided by an experienced Intensive Care doctor/ACCP. Use local DKA trust guidelines as a starting point but consider cardiac output/FICE guided resuscitation if acidosis or hypotension fail to respond.

Canagliflozin, dapagliflozin or empagliflozin should be held on admission to critical care and not restarted until discharge from critical care and eGFR over 60. They should be omitted for at least 72 hours before patients undergo elective surgery.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors:
Canagliflozin, Dapagliflozin & Empagliflozin
Reversibly inhibit sodium-glucose co-transporter 2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion. Indicated for use in Type 2 diabetes and congestive cardiac failure.



SGLT-2 inhibitors are associated with a risk euglycemic ketoacidosis that may exist for several days after discontinuation of treatment. This is a particular risk to critically ill patients and those patients that have a sudden reduction in calorie intake (e.g vomiting secondary to gastroenteritis). Unexplained acidosis in a patient admitted who has been taking a SGLT-2 inhibitor should prompt investigation for ketoacidosis even in the context of normal glucose levels.

Patients should have their SGLT-2 inhibitors held for a minimum of 72 hours preoperatively. If continued before surgery then ensure nutrition (glucose maintenance containing fluid)

5.8 Sulphonylureas

- The sulphonylureas (gliclazide and glimepiride) cause insulin release by direct binding to receptors on beta cells. They are associated with hypoglycaemia. Critically ill patients with unpredictable absorption and renal clearance may be at higher risk.

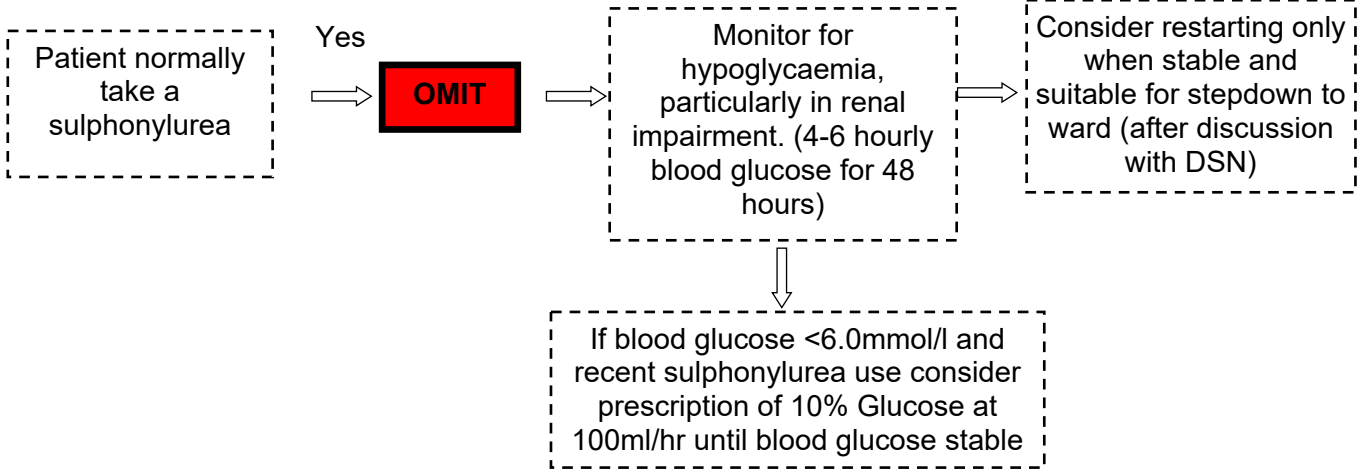
- Gliclazide and glimepiride should be suspended on admission to critical care and blood glucose should be monitored closely (every 4-6 hours) for up to 48 hours if the patient has any evidence of renal impairment.

- If blood glucose is found to be below 6mmol/l in a patient who has been taking sulphonylureas prior to admission to critical care, check HbA1c if not recently done, and consider starting a background glucose infusion until full feed is established to minimise the risk of a hypoglycaemia. Target blood glucose range in patients on insulin secretagogues is 6-12mmol/l – sulponylureas should be discontinued if blood glucose is less than 6mmol/l.

- Gliclazide may be recommended as first line in the Trust Steroid Induced Hyperglycaemia guideline and this would be appropriate in certain patient groups (e.g steroids started for level 2 patients admitted for post operative monitoring, autoimmune conditions etc).

- Sulphonylureas should not be restarted until the patient is well enough to discharge to ward level care, is eating or has enteral route established. They may be considered in certain patients with Type 2 Diabetes e.g. prolonged tracheostomy wean with single organ support.

Sulphonylureas: Gliclazide/ Glimepiride
bind to receptors on Beta cells causing increased release of insulin



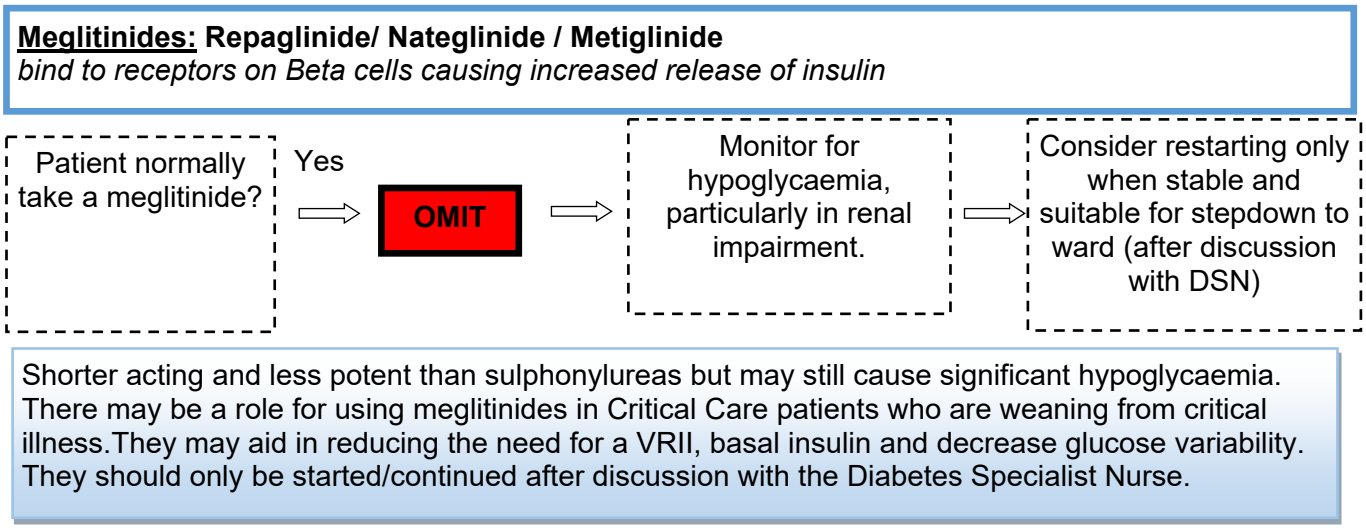
High risk for hypoglycaemia in critically ill patients and in those with drug accumulation in renal failure.
Multiple drug interactions
There may be a role for using gliclazides in Critical Care patients who are weaning from critical illness. They may aid in reducing the need for a VRII, basal insulin and decrease glucose variability. Gliclazide is indicated as first line management in SCO guidelines for steroid induced hyperglycaemia. In critically ill patients they are less likely to be effective in this situation and IV insulin may be preferable.
They should only be started/continued after discussion with the Diabetes Specialist Nurse.

5.9 Meglitinides

- Repaglinide and nateglinide act in a similar manner to the sulphonylureas (bind to beta cells causing insulin release). They are less potent and have a shorter duration of action than sulphonylureas but still may pose a risk of hypoglycaemia.

- Repaglinide and nateglinide should be suspended on admission to critical care and blood glucose should be monitored closely (every 4-6 hours) for up to 48 hours if the patient has any evidence of renal impairment.

- Meglitinides should not be restarted until the patient is well enough to discharge to ward level care and is eating or has enteral route established. They may be considered in certain patients with Type 2 Diabetes e.g., prolonged ventilatory wean with single organ support.



Shorter acting and less potent than sulphonylureas but may still cause significant hypoglycaemia. There may be a role for using meglitinides in Critical Care patients who are weaning from critical illness.They may aid in reducing the need for a VRII, basal insulin and decrease glucose variability. They should only be started/continued after discussion with the Diabetes Specialist Nurse.

5.10 Thiazolidinediones

- Thiazolidinediones act via nuclear receptors (and therefore by effects on gene transcription) to increase free fatty acid uptake into adipocytes which results in an increase in glucose metabolism.

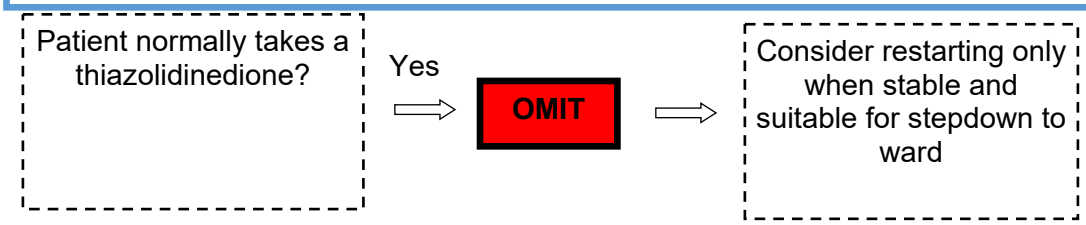
- This action at nuclear receptors results in a markedly prolonged duration of action even after the drug is discontinued.

- They are associated with an increased risk of hypoglycaemia in association with insulin/sulfonylureas and in chronic use associated with peripheral oedema, fluid retention and exacerbation of congestive cardiac failure.

- Thiazolidinediones should be suspended on admission to critical care and blood glucose should be monitored closely (every 4-6 hours) for up to 48 hours if the patient has any evidence of renal impairment.

- Thiazolidinediones should not be restarted until the patient is well enough to discharge to ward level care, is eating or has enteral route established and has been reviewed by the Diabetes Specialist nurse.

Thiazolidinediones: Pioglitazone / Rosiglitazome
Bind to nuclear receptors increasing uptake of free fatty acids into adipocytes resulting in increased glucose metabolism

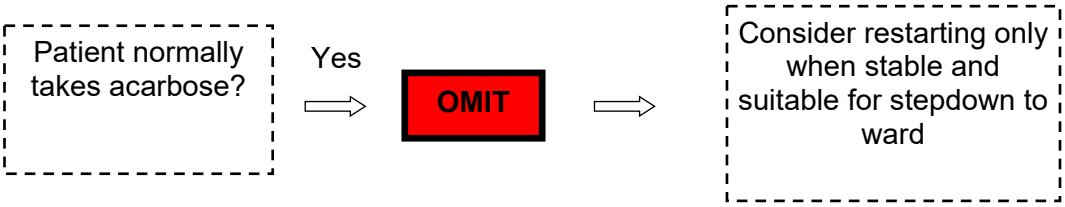


Can cause fluid retention, peripheral oedema and worsen congestive cardiac failure.
Pharmacological actions are via nuclear binding receptors so hypoglycaemia can occur in fasting patients many days after stopping therapy.
Should be discontinued whilst in critical care

5.11 Alpha glucosidase inhibitors

- Acarbose inhibits the intestinal brush border enzymes and reduces glucose absorption. They are associated with gastrointestinal upset and should not be used in patients in critical care.

Alpha-glucosidase inhibitors: Acarbose
Intestinal brush border enzyme inhibitor



Likely to cause GI disturbance and diarrhoea.
Omit whilst on critical care

5.12 Hypoglycaemia

Appendix 3: see Hypoglycaemia algorithm

- Avoidance of hypoglycaemia is of high priority in patients being treated for hyperglycaemia on critical care.

- Hypoglycaemia is associated with a significantly elevated risk of mortality in critically ill patients and this effect has been shown to be associated with the severity and number of hypoglycaemic episodes.

- Hypoglycaemia may be absolute or relative. Patients with pre-existing diabetes with poor control may exhibit cardiovascular, hormonal, and neurological changes at low-normal levels. Aggressively targeting blood glucose in the “normal” range may be harmful in these patients.

- Minimising hypoglycaemia in critical care depends on three aims:
    - Avoidance
    - Treatment
    - & Learning from Hypoglycaemia
    -

5.5.1 Avoidance of Hypoglycaemia

- Monitoring of blood glucose should be 1 hourly when on an insulin infusion.

- If blood glucose has been stable and between 6 – 10mmol/l for 2 consecutive hours this may be extended to 2 hourly checks.

- **Looming Hypoglycaemia.** Monitoring frequency should increase to every 30 minutes if blood glucose has dropped below 6.0mmol/l and on an insulin infusion until glucose has been demonstrably stable above 6.0mmol/l for 2 hours (insulin infusion will have been discontinued according to protocol at this stage).

- It is recognised that this increased monitoring frequency is not always achievable when there are competing clinical pressures and whilst these guidelines represent ideal practice their purpose is to draw attention to the increased risk of hypoglycaemia when blood glucose drops below 6.0mmol/l.

- Once hypoglycaemia is identified < 4.0mmol/l and treatment commenced, blood glucose should be rechecked at 15, 30 and 60 minutes.

- Blood glucose should be monitored every 4 hours when on a long-acting subcutaneous insulin regardless of mode of nutrition.

- For transfer to scan, insulin should be discontinued for the duration of the transfer – refer to hypoglycaemia algorithm. Monitoring of blood glucose should be continued as per guidelines in this document.

- The choice of maintenance replacement fluid should be at the discretion of the caring physician according to departmental guidelines. It should be tailored to the patient's clinical presentation but ***must be glucose containing if intravenous insulin has been used in the last 4 hours***. Unopposed intravenous insulin creates a risk of iatrogenic hypoglycaemia and should be avoided. However, the use of glucose containing fluids may in themselves cause iatrogenic hyperglycaemia and this should prompt the physician to review the need for IV insulin in these patients. If an assessment is made that (e.g.) low sodium containing maintenance fluid is contraindicated and IV insulin is required to control hyperglycaemia without a source of nutrition, this should be discussed with the bedside nurse and documented clearly as part of treatment goals.

5.5.2 Treatment of Hypoglycaemia

- Management of an episode of hypoglycaemia in the critical care should be according to a treatment protocol that is weighted differently to ward areas. This reflects the patient population being less likely to be conscious and able to report hypoglycaemia symptoms and the likelihood of central venous access making the use of 50% glucose safe and more practical. The treatment should still consist of 15-25g fast acting carbohydrate.

- Management should consist of a step wise protocol (see algorithm).
- Treatment should be initiated if blood glucose < 4.0mmol/l

    - Central line access: give 50ml 50% glucose immediately.
    - No central line but peripheral access: give 250ml 10% glucose immediately.
    - No central or peripheral access: give 2 tubes of GlucoGel administered via the gums or glucagon 1mg IV/SC/IM.

- To ensure immediate access to these treatments any patient starting on an insulin infusion in critical care shall have the ***3 glucose preparations prescribed on the PRN side of the chart***.

5.5.3 Learning from Hypoglycaemia

- It should be recognised that hypoglycaemia is a common and sometimes unavoidable side effect of glucose management in the Critical Care Unit. The causes of hypoglycaemia are multifactorial. Steps should be taken to minimise further episodes where possible.

- Any episode of hypoglycaemia in critical care (< 4.0mmol/l) should be reported via the Hospital Incident Reporting System.

Blood glucose values recorded in the ABG analysers and POC machines can be accessed and used to review the management of both hyperglycaemia and hypoglycaemia. A structured review of hypoglycaemia episodes should be undertaken every 3 months and report issued to aid education and aid with protocol redevelopment.

Hypoglycaemia Protocol in Critical Care

AVOIDANCE

Looming Hypoglycaemia
Blood glucose < 6.0 mmol/l on an insulin infusion?
STOP INSULIN INFUSION
Recheck in 30 minutes and 1 hour

Risk Factors

1. Not checking blood glucose frequently enough
IV insulin—every hour
Subcutaneous insulin—every 4 hours

2. Interruptions in nutrition
Feed breaks/displaced NGT/fasting for procedures or scans. Ensure IV glucose as an alternative and stop IV insulin if no nutrition.

3. Medication change (check long-acting insulins)

4. Resolving critical illness & drug excretion

TREATMENT

Blood Glucose < 4.0 mmol/l
Four is the Floor—Treat Immediately
STOP INSULIN INFUSION!

Recheck blood glucose at 15, 30 and 60 minutes or until >4.0mmol/l

Does the patient have a central line?
Yes → **50ml of 50% glucose via CVC line over 10 minutes (followed immediately by 0.9% NaCl flush**

No

Does the patient have a peripheral cannula?
Yes → **250ml of 10% glucose via a peripheral cannula over 15 minutes**

No

Is there an enteral route?
Yes → **200ml orange juice or 6 glucose tablets PO or crushed down NG + 1mg Glucagon IM**

No → **2 tubes of Glucogel via gums + 1mg Glucagon IM**

LEARNING

Hypoglycaemia is a risk in ICU patients, take steps to improve future management
- Document the episode: include details of insulin, oral medications, nutrition etc
- Review risk factors to avoid a further episode
- Discuss on next Handover & Ward Round— review insulin treatment

Episode of hypoglycaemia (<4.0mmol/l) in a critical care patient: complete Incident form. Regular audit of hypoglycaemia episodes

6. Roles & Responsibilities

6.1 Clinical Staff including Doctors, Advanced practitioners, and pharmacists

Clinical staff looking after the patient:

- Diabetic management to be reviewed daily and discussed on daily ward round.
- Where individualised patient therapy requires deviation from the guidelines, reasons should be documented in the patients notes.
- Any patient who experiences any other harm from diabetes treatment should have a DATIX adverse incident report submitted, this includes all episodes of hypogylcaemia in critical care.

6.2 Nursing staff

Nursing staff looking after the patient will:

- Ensure Diabetes treatments are administered as prescribed in a timely manner.
- Ensure that blood glucose monitoring and all other relevant documentation are completed accurately for all patients on diabetes treatments.
- Any patient who experiences any other harm from diabetes treatment should have a DATIX adverse incident report submitted.

6.3 Ward Manager

- Ensure that critical care staff caring for patients following this treatment are aware of and comply with the guideline.
- Address any competency issues.

6.4 Individual responsibility

- Individual staff members are responsible for identifying gaps in their knowledge, and their training needs to enable the management of patients using this treatment.

7. Monitoring Document Effectiveness

Key standards:

- All Diabetes management strategies should be prescribed and reviewed daily.
- No verbal orders for diabetes strategies are allowed.
- Document a diabetes management plan every 24 hours during working days.
- All staff involved in diabetes management should receive appropriate training.
  For medical prescribers this is part of induction.
  For non-medical prescribers this is part of annual update.
  For administrators, this is part of Medicines Management Mandatory training.

Method: A clinical audit

- **Team responsible for monitoring:** Pharmacy and medical team, will use existing audit as a baseline, and will continue to use the same audit tool to acquire blood glucose results from the biochemistry labs.
- **Frequency of monitoring:** once a year

- **Process for reviewing results and ensuring improvements in performance:** Results of audit will be presented at the audit meeting and discussed with the MDT.

A new clinical audit tool will be developed to undertake annual audit of adherence to the guidelines.

8. Abbreviations & Definitions

List all abbreviations or acronyms:

ABG	Arterial Blood Gas
ANP / ACCP	Advanced Nurse Practitioner / Advanced Critical Care Practioner
bd	Twice daily
BG	Blood glucose
CVVHF	Continuous Veno-Veneous Hemofiltration
DKA	Diabetic Ketoacidosis
DSN	Diabetes Specialist Nurse
EC	Enteric coated
HbA1c	Glycated Haemoglobin
hr	Hour
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
l	Litre
ml	Millilitre
mmol	Millimole
mol	Mole
POC	Point of Care
s/c	Subcutaneous
PN	Parenteral Nutrition
VBG	Venous Blood Gas
FRII	Fixed Rate Insulin Infusion
VRII	Variable Rate Insulin Infusion

9. References

Gupta, K. J. and T. M. Cook "Accidental hypoglycaemia caused by an arterial flush drug error: a case report and contributory causes analysis." Anaesthesia **68**(11): 1179-1187.

Inoue, Shigeaki, Moritoki Egi, Joji Kotani, and Kiyoshi Morita. “Accuracy of Blood-Glucose Measurements Using Glucose Meters and Arterial Blood Gas Analyzers in Critically Ill Adult Patients: Systematic Review.” *Critical Care* 17, no. 2 (2013): R48. https://doi.org/10.1186/cc12567.

“Fatal Neuroglycopaenia after Accidental Use of a Glucose 5% Solution in a Peripheral Arterial Cannula Flush System - Sinha - 2007 - Anaesthesia - Wiley Online Library.” Accessed October 3, 2018. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2044.2007.04989.x.

Finfer, Simon, Jan Wernerman, Jean-Charles Preiser, Tony Cass, Thomas Desaive, Roman Hovorka, Jeffrey I Joseph, et al. “Clinical Review: Consensus Recommendations on Measurement of Blood Glucose and Reporting Glycemic Control in Critically Ill Adults.” *Critical Care* 17, no. 3 (2013): 229. https://doi.org/10.1186/cc12537.

Jacobi, Judith, Nicholas Bircher, James Krinsley, Michael Agus, Susan S. Braithwaite, Clifford Deutschman, Amado X. Freire, et al. “Guidelines for the Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients:” *Critical Care Medicine* 40, no. 12 (December 2012): 3251–76. https://doi.org/10.1097/CCM.0b013e3182653269.

Dhatariya, K., N. Levy, A. Kilvert, B. Watson, D. Cousins, D. Flanagan, L. Hilton, et al. “NHS Diabetes Guideline for the Perioperative Management of the Adult Patient with Diabetes*.” *Diabetic Medicine* 29, no. 4 (April 1, 2012): 420–33. https://doi.org/10.1111/j.1464-5491.2012.03582.x.

“Use of Variable Rate Intravenous Insulin Infusion in Medical Inpatients_0.Pdf.” Accessed August 22, 2018. https://www.diabetes.org.uk/resources-s3/2017-09/Use%20of%20variable%20rate%20intravenous%20insulin%20infusion%20in%20medical%20inpatients_0.pdf.

Krinsley, James S., Moritoki Egi, Alex Kiss, Amin N. Devendra, Philipp Schuetz, Paula M. Maurer, Marcus J. Schultz, et al. “Diabetic Status and the Relation of the Three Domains of Glycemic Control Tomortality in Critically Ill Patients: An International Multicenter Cohort Study.” *Critical Care* 17, no. 2 (March 1, 2013): R37. https://doi.org/10.1186/cc12547.

Krinsley, James S., Moritoki Egi, Alex Kiss, Amin N. Devendra, Philipp Schuetz, Paula M. Maurer, Marcus J. Schultz, et al. “Diabetic Status and the Relation of the Three Domains of Glycemic Control Tomortality in Critically Ill Patients: An International Multicenter Cohort Study.” *Critical Care* 17, no. 2 (March 1, 2013): R37. https://doi.org/10.1186/cc12547.

Rostami, Elham. “Glucose and the Injured Brain-Monitored in the Neurointensive Care Unit.” *Frontiers in Neurology* 5 (June 6, 2014). https://doi.org/10.3389/fneur.2014.00091.

Vespa, Paul, Robert Boonyaputthikul, David L. McArthur, Chad Miller, Maria Etchepare, Marvin Bergsneider, Thomas Glenn, Neil Martin, and David Hovda. “Intensive Insulin Therapy Reduces Microdialysis Glucose Values without Altering Glucose Utilization or Improving the Lactate/Pyruvate Ratio after Traumatic Brain Injury*:” *Critical Care Medicine* 34, no. 3 (March 2006): 850–56. https://doi.org/10.1097/01.CCM.0000201875.12245.6F.

Rommers, Mirjam K., Netty Van Der Lely, Toine CG Egberts, and Patricia MLA van den Bemt. “Anti-Xa Activity after Subcutaneous Administration of Dalteparin in ICU Patients with and without Subcutaneous Oedema: A Pilot Study.” *Critical Care* 10, no. 3 (June 21, 2006): R93. https://doi.org/10.1186/cc4952.

Salpeter, Shelley R., Elizabeth Greyber, Gary A. Pasternak, and Edwin E. Salpeter (posthumous). “Risk of Fatal and Nonfatal Lactic Acidosis with Metformin Use in Type 2 Diabetes Mellitus.” *Cochrane Database of Systematic Reviews*, no. 1 (2010). https://doi.org/10.1002/14651858.CD002967.pub3.

Christiansen, Christian Fynbo, Martin Berg Johansen, Steffen Christensen, James M. O’Brien, Else Tønnesen, and Henrik Toft Sørensen. “Preadmission Metformin Use and Mortality among Intensive Care Patients with Diabetes: A Cohort Study.” *Critical Care* 17, no. 5 (September 9, 2013): R192. https://doi.org/10.1186/cc12886.

Jochmans, Sebastien, Jean-Emmanuel Alphonsine, Jonathan Chelly, Ly Van Phach Vong, Oumar Sy, Nathalie Rolin, Olivier Ellrodt, Mehran Monchi, and Christophe Vinsonneau. “Does Metformin Exposure before ICU Stay Have Any Impact on Patients’ Outcome? A Retrospective Cohort Study of Diabetic Patients.” *Annals of Intensive Care* 7 (December 2, 2017). https://doi.org/10.1186/s13613-017-0336-8.

Verma, Vishesh, Narendra Kotwal, Vimal Upreti, Monish Nakra, Yashpal Singh, K. Anand Shankar, Amit Nachankar, and K.V.S. Hari Kumar. “Liraglutide as an Alternative to Insulin for Glycemic Control in Intensive Care Unit: A Randomized, Open-Label, Clinical Study.” *Indian Journal of Critical Care Medicine : Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine* 21, no. 9 (September 2017): 568–72. https://doi.org/10.4103/ijccm.IJCCM_105_17.

Abuannadi, Mohammad, Mikhail Kosiborod, Lisa Riggs, John A. House, Mitchell S. Hamburg, Kevin F. Kennedy, and Steven P. Marso. “Management of Hyperglycemia with the Administration of Intravenous Exenatide to Patients in the Cardiac Intensive Care Unit.” *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 19, no. 1 (February 2013): 81–90. https://doi.org/10.4158/EP12196.OR.

Plummer, Mark P, Marianne J Chapman, Michael Horowitz, and Adam M Deane. “Incretins and the Intensivist: What Are They and What Does an Intensivist Need to Know about Them?” *Critical Care* 18, no. 1 (2014). https://doi.org/10.1186/cc13737.

Zinman, Bernard, Christoph Wanner, John M. Lachin, David Fitchett, Erich Bluhmki, Stefan Hantel, Michaela Mattheus, et al. “Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.” *New England Journal of Medicine* 373, no. 22 (November 26, 2015): 2117–28. https://doi.org/10.1056/NEJMoa1504720.

Garg, Satish K., Robert R. Henry, Phillip Banks, John B. Buse, Melanie J. Davies, Gregory R. Fulcher, Paolo Pozzilli, et al. “Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes.” *New England Journal of Medicine* 377, no. 24 (December 14, 2017): 2337–48. https://doi.org/10.1056/NEJMoa1708337.

Excellence, NICE-The National Institute for Health and Care. “BNF: British National Formulary - NICE.” CorporatePage. Accessed September 17, 2018. https://bnf.nice.org.uk/drug/canagliflozin.html.

Hypoglycemia and Risk of Death in Critically Ill Patients | NEJM.” Accessed August 15, 2018. https://www.nejm.org/doi/full/10.1056/NEJMoa1204942.
Arabi, Yaseen M., Hani M. Tamim, and Asgar H. Rishu. “Hypoglycemia with Intensive Insulin Therapy in Critically Ill Patients: Predisposing Factors and Association with Mortality*:” *Critical Care Medicine* 37, no. 9 (September 2009): 2536–44. https://doi.org/10.1097/CCM.0b013e3181a381ad.

Poole AP, Finnis ME, Anstey J, Bellomo R, Bihari S, Biradar V, Doherty S, Eastwood G, Finfer S, French CJ, Heller S, Horowitz M, Kar P, Kruger PS, Maiden MJ, Mårtensson J, McArthur CJ, McGuinness SP, Secombe PJ, Tobin AE, Udy AA, Young PJ, Deane AM; LUCID Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). The Effect of a Liberal Approach to Glucose Control in Critically Ill Patients with

Type 2 Diabetes: A Multicenter, Parallel-Group, Open-Label Randomized Clinical Trial. Am J Respir Crit Care Med. 2022 Oct 1;206(7):874-882. doi: 10.1164/rccm.202202-0329OC. PMID: 35608484.

Bohé J, Abidi H, Brunot V, Klich A, Klouche K, Sedillot N, Tchenio X, Quenot JP, Roudaut JB, Mottard N, Thiollière F, Dellamonica J, Wallet F, Souweine B, Lautrette A, Preiser JC, Timsit JF, Vacheron CH, Ait Hssain A, Maucort-Boulch D; CONTROLe INdividualisé de la Glycémie (CONTROLING) Study Group. Individualised versus conventional glucose control in critically-ill patients: the CONTROLING study-a randomized clinical trial. Intensive Care Med. 2021 Nov;47(11):1271-1283. doi: 10.1007/s00134-021-06526-8. Epub 2021 Sep 29. PMID: 34590159; PMCID: PMC8550173.

Gunst el at. Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU N Engl J Med 2023; 389:1180-1190 DOI: 10.1056/NEJMoa2304855

10. Document Control Information

Part 1: Lead Author, Consultation Details, Communication Plan

Must be fully completed by the author prior to submission for approval.

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Job title	Consultant in Intensive Care Medicine & Anaesthesia
Contact number	
Email address	Rhodri.harris@nca.nhs.uk

Consultation: List persons/group included in consultation. Include Pharmacy/Medicine Optimisation Group (MOG) for documents containing drugs. Indicate whether feedback used/ received and no suggested changes (FU), not used (FNU) or not received (NR).

Name/s of person or group	State which Care Organisations/ corporate services/staff groups the person or group represents	Date	Response: FU/FNU/NR
Diabetes Specialist Team Ascia Bibi	Oldham / Bury CO	Dec 2023	FU
Diabetes Specialist Team Louise Wong, Rebecca Makin Dr Angela Paisley (Consultant in Diabetes & Endocrinology, SCO)	Salford CO	Dec 2023	FU
Critical Care Unit Medical/Pharmacy Emma Boxall	Salford & Bury CCU	Jan 2024	FU
Critical Care Unit Medical/Pharmacy Nagaraja Ravishankar, Rukhsana Mahmood	Oldham CCU	Jan 2024	FU
Medicines Optimisation Group	NCA	July 2024	FU

Equality Impact Assessment sign off: See Section 11.

Name (Lead from EDI team)	Emma Davenport
Date	05/06/2024

Communication plan: State in the box below how practice in this document will be rolled out across the organisation and embedded. A communication plan may be requested for review by the approving committee – if applicable, add owner details.

Email communication to critical care doctors and pharmacists at the point of publication to the Policy hub. Signposting from the online resources at saferinsulin.org to the hub site. Education drive with safety topic of the week and training with practice educators.

Part 2: Committee Approval

Must be fully completed by the author following committee approval. Failure to complete fully will potentially delay publication of the document. Submit to the Document Control Team at document.control@nca.nhs.uk for publication.

Approval date	18/7/24
Method of approval (delete as appropriate)	Formal Committee decision / Chairperson's approval
Name of approving Committee	Medicines Optimisation Committee
Chairperson Name / Role	Daine Elford, Lead Clinical Pharmacist Medicine
Amendments approval: Name of approver, version number and date. Do not amend above details	

Part 3: Search Terms and Review Arrangements

Must be fully completed by the author prior to publication.

Keywords & phrases	Critical Care, Glucose, Hyperglycaemia, Hypoglyaemia, ICU,
Document review arrangements	Review will occur by the author, or a nominated person, within three years or earlier should a change in legislation, best practice, or other change in circumstance dictate.
Special requests	Indicate whether upon publication you require specific groups to be informed such as nursing or medical? This will be in addition to the policy author.

11. Equality Impact Assessment (EqIA) tool

- The below tool must be completed at the start of any new or existing policy, procedure, or guideline development or review. For ease, all documents will be referred to as 'policy'. The EqIA should be used to inform the design of the new policy and reviewed right up until the policy is approved and not completed simply as an audit of the final policy itself.
- All sections of the tool will expand as required.
- EqIAs must be sent for review prior to the policy being sent to committee for approval. Any changes made at committee after an EqIA has been signed off must result in the EqIA being updated to reflect these changes. Policies will not be published without a completed and quality reviewed EqIA.

Help and guidance available:

- Equality Impact Assessment Help Resource
- Email the EDI Team: eqia@nca.nhs.uk for advice or training information.
- Submit documents requiring EqIA sign off to: eqia@nca.nhs.uk. Allow an initial four-week turnaround.
- Where there is a statutory or significant risk, requests to expedite the review process can be made by exception to the Group Equality & Inclusion Programme Manager: Yasmin.bukhari@nca.nhs.uk

Part 1: Possible Negative Impacts

Protected Characteristic	Possible Impact	Action/Mitigation
Age	Adult patients only	Written for adult ICU patients, although may be suitable for paediatrics in considered cases.
Disability	No impact	
Ethnicity	No impact	
Gender	No impact	
Marriage/Civil Partnership	No impact	
Pregnancy/Maternity	No impact	
Religion & Belief	No impact	
Sexual Orientation	No impact	
Trans	No impact	
Other Under Served Communities (Including Carers, Low Income, Veterans)	Carers not involved in communication	To be involved/updated at all times

Part 2: Possible Opportunity for Positive Impacts

Protected Characteristic	Possible Impact	Action/Mitigation
Age	Positive impact for all patients with protected characteristics through the standardisation of management of blood glucose control in adult critical care patients.	
Disability	Persons with diabetes	Written to improve care for this patient group
Ethnicity		
Gender		
Marriage/Civil Partnership		
Pregnancy/Maternity		
Religion & Belief		
Sexual Orientation		
Trans		
Other Under Served Communities (Including Carers, Low Income, Veterans)		

Part 3: Combined Action Plan

Action *(List all actions & mitigation below)*	Due Date	Lead *(Name & Job Role)*	From Negative or Positive Impact?
No actions identified.			

Part 4: Information Consulted and Evidence Base *(Including any consultation)*

Protected Characteristic	Name of Source	Summary of Areas Covered	Web link/contact info
Age			
Disability			
Ethnicity			
Gender			
Marriage/Civil Partnership			
Pregnancy/Maternity			
Religion & Belief			
Sexual Orientation			
Trans			
Other Under Served Communities (Including Carers, Low Income, Veterans)			

Part 5: EqIA Update Log (Detail any changes made to EqIA as policy has developed and any additional impacts included)

Date of Update	Author of Update	Change Made
April 2024	Rhodri Harris	EqIA updated.

6. Have all of the negative impacts you have considered been fully mitigated or resolved? *(If the answer is no, please explain how these don't constitute a breach of the Equality Act 2010 or the Human Rights Act 1998)*
Yes, this policy has been written for adult ICU patients, although may be suitable for paediatrics in considered cases. No other negative impacts identified.

7. Please explain how you have considered the duties under the accessible information standard if your document relates to patients?
This policy is for NCA colleague use only and will be published in an accessible format.

8. Equality Impact Assessment completed and signed off? *(Insert named lead from EDI Team below). Please also add this information to Section 10 Part 1.*
Name: Emma Davenport **Date:** 05/06/2024