Manchester University
NHS Foundation Trust

DOCUMENT CONTROL PAGE	
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1. Detail of Procedural Document.

These guidelines and are designed to be used only on patients admitted to the Critical Care Units across MFT.

Key Principles

- 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

- Avoidance of hyperglycaemia is desirable and the ***treatment threshold above which insulin should be commence is 10mmol/l with a target range of 6.0-10mmol/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

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

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

- It is likely that patients should have an individualised glucose target according to their history of diabetes, chronic glucose control and the nature of their presenting critical illness. However, until future randomised controlled trials are available, the best evidence supports using a “conventional” rather than intensive treatment strategy with a focus on avoiding hypoglycaemia and glycaemic variability

- 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 diagnosed using glucose tests

- Certain patient groups such as post-organ transplant will require specialist input and the Trust Diabetes Team should be involved at the earliest opportunity. The key principles of these guidelines may be used in the early stage of their critical illness but should not replace specialist protocols.

- Elective surgical patients admitted to critical care with diabetes should follow the perioperative diabetes management guidelines
- 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 the critically ill patient. This document aims to provide guidance on the use of these agents in the critical care unit

- Critical care patients have unpredictable absorption of subcutaneous insulin and this may pose a risk of both under and overdosing of insulin

Hyperglycaemia

See appendix 1: Hyperglycaemia algorithm

Monitoring of blood glucose levels

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

- 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 / ANP 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. Similarly, POC capillary glucose is the least accurate method and an unexpectedly abnormal sample should be checked against an arterial or venous ABG or laboratory serum glucose sample.

- If a Variable Rate Insulin Infusion is commenced, then blood glucose should be checked 1 hourly ideally via ABG / VBG but POC Capillary Sampling is acceptable if patient's glucose control has been stable over the preceding 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 Variable Rate Insulin Infusion is being stopped or is no longer required blood glucose should be monitored hourly for at least 2 hours post stopping. This is particularly relevant when stopping for procedures or scans

Target blood glucose range

- A Variable Rate Insulin Infusion (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 is 6.0-10mmol/l

- 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

Commencing a Variable Rate Insulin Infusion (VRII)

See Appendix 2: VRII protocols

- A VRII should be commenced according to the initial glucose reading using the table in the VRII protocol

- It is envisaged that the starting regimen for most patients will be Scale A and the scale must be signed by the clinical team

- Clinicians may choose to start with Scale B e.g. if a patient is obese (>100kg) or insulin resistant (>100 units/day)

- Over the next 12 – 18 months we plan to move over to an insulin infusion via a Dynamic Sliding Scale using an insulin calculator. Until this is available, we will continue to use the paper based Variable Rate Insulin Infusion modified for use in Critical Care (see appendix)

- Insulin Actrapid 50 units 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**.** Insulin preparations should be replaced every 24 hours to minimise the loss of potency

Basal Insulin, Oral and Novel Antidiabetic Agents

Basal / Long acting Insulin

- Patients with Type 1 Diabetes should continue their normal (100%) basal insulin dose ensuring patient is receiving enteral feed, TPN or a dextrose containing fluid

- Patients with an insulin pump should in general 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

- Patients with Type 2 Diabetes should aim to have their basal insulin prescribed at 80% of their normal dose, once they have been established on enteral or TPN feed.

- If there is any doubt about patient's normal dose or compliance, then consider Levemir 10units sc bd starting dose and/or discuss with the diabetes team first

- Non-diabetic patients (or those not previously diagnosed) who have been on a VRII for more than 24 hours and who have been established on enteral or TPN feed can be considered for basal subcutaneous insulin. This should be 50% of total daily insulin requirement (previous 24 hours) split into 2 doses e.g. Levemir – maximum 10units bd starting dose. Discuss with the diabetes team

- Increases of basal insulin doses should be gradual (ideally every 48-72 hours) and not by more than 50% of the current dose. This may be modified after review by the Diabetes Specialist Nurse

- Basal 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

- Basal insulin should not be started for patients in critical care who are felt to have hyperglycaemia secondary to steroid use or in whom HBA1c < 53mmol/l and are non-diabetic. Hyperglycaemia is likely to be transient and resolve with stopping steroids or when critical illness resolves. Please consult the diabetes team if any queries on this point

- 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 range (6.0-10.0mmol/l)

Basal / Long Acting Insulin

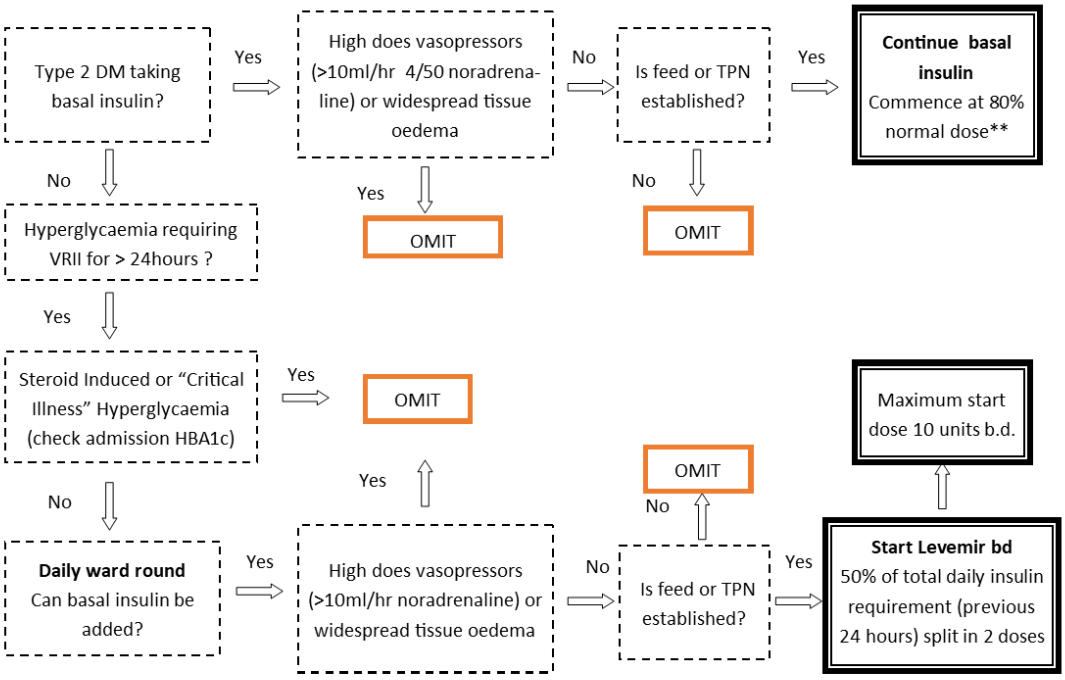
Patients with Type 1 Diabetes should continue their normal (100%) basal insulin dose ensuring patient is receiving enteral feed, TPN or a dextrose containing fluid

Lantus, Toujeo & Abasalgar (insulin glargine) duration 24hours

Levemir (insulin detemir) duration 12-24 hours

Tresiba (insulin degludec) duration 42 hours

Long acting insulins may be given once or twice daily via subcutaneous injection.



Target range on subcutaneous insulin **6.0-10mmol/l**

Subcutaneous absorption affected by vasopressors, oedema and critical illness

Clearance affected by renal impairment and changes in renal function and in hepatic impairment

** Accurate reporting of patient's preadmission basal insulin dose may be difficult and compliance is often variable. For this reason commence at 80% reported dose in tye 2 DM and increase over 48 hours when a blood glucose trend is established and calorie intake has increased. If any uncertainty regarding compliance or not clear what normal dose is start Levemir 10units bd s/c

Dose adjustments should be gradual (every 2-3 days) and ideally led by Diabetes Specialist Nurse

If hyperglycaemia secondary to steroid therapy **do not** start basal subcutaneous insulin, treat with temporary IV infusion only

Basal 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 dependednt oedema occurs, the upper arm may be preferable.

Metformin

- Metformin may be associated with lactic acidosis in critically ill patients with shock, hepatic impairment or acute and chronic renal failure

- Metformin should be suspended in patients with:

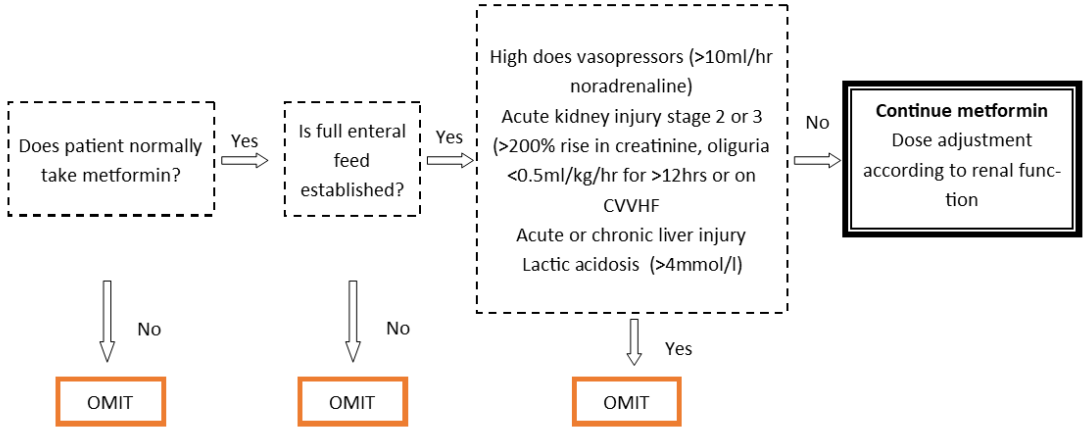
    - No enteral route / surgical contraindication
    - Shock requiring > 10ml/hr (4/50) noradrenaline or equivalent
    - Acute or chronic liver failure
    - Acute kidney injury (AKIN) Stage 2 or 3 (increase serum creatinine >200%, urine output < 0.5ml/kg/hr for >12hrs or on renal replacement therapy)

- 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 adjusted according to eGFR in chronic renal failure or stable AKI / on CVVHF

Metformin

Biguanide: decreases hepatic glucose production and increases peripheral glucose uptake



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 4mmol/l omit metformin.

Glucose-like-peptide (GLP) 1 Analogues

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

- The GLP1 analogues (exenatide and liraglutide) 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

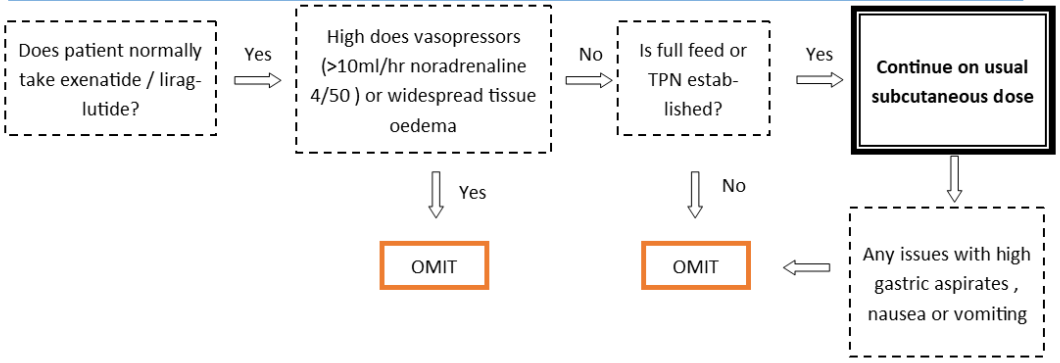
- Exenatide has been demonstrated to be an effective agent in controlling blood glucose in critically ill patients but it's use at high doses was limited by gastrointestinal side effects. In the absence of high gastric aspirates or nausea these agents can be safely continued in patients who are already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

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. They should be discontinued in high gastric aspirates, nausea or vomiting

Exenatide / Liraglutide

Glucagon-like peptide-1 (GLP-1) agonists: Subcutaneous injection. Incretin mimetic, blocks glucagon release, increases insulin release to glucose

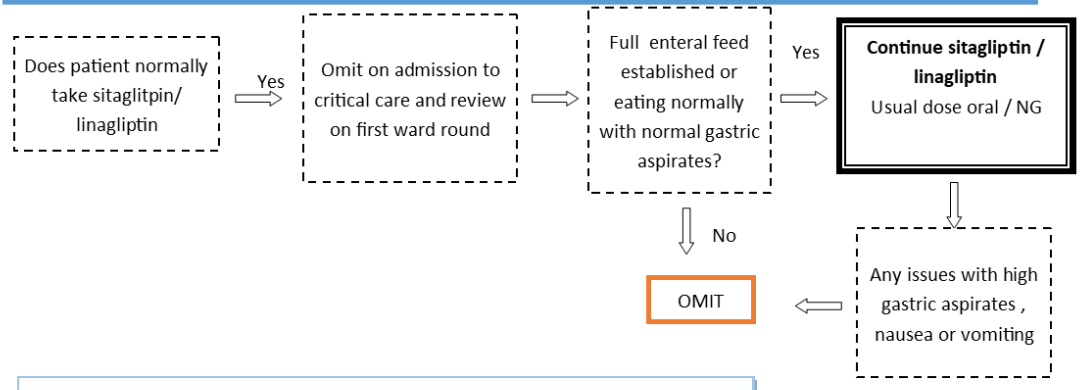


Exanatide and liraglutide cause delayed gastric emptying (and therefore reduce postprandial hyperglycaemia). This may cause problems with absorbing NG feed. Should be stopped in patients with high GI aspirates

Less risk of hypoglycaemia than other antidiabetic agents

Sitagliptin / Linagliptin

Dipeptidyl peptidase-4 (DPP-4) inhibitors: Oral medication. Increase incretin levels therefore suppress glucagon release.



May be associated with GI disturbance, nausea, vomiting

Rare reports of pancreatitis

Less risk of hypoglycaemia than other antidiabetic agents

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

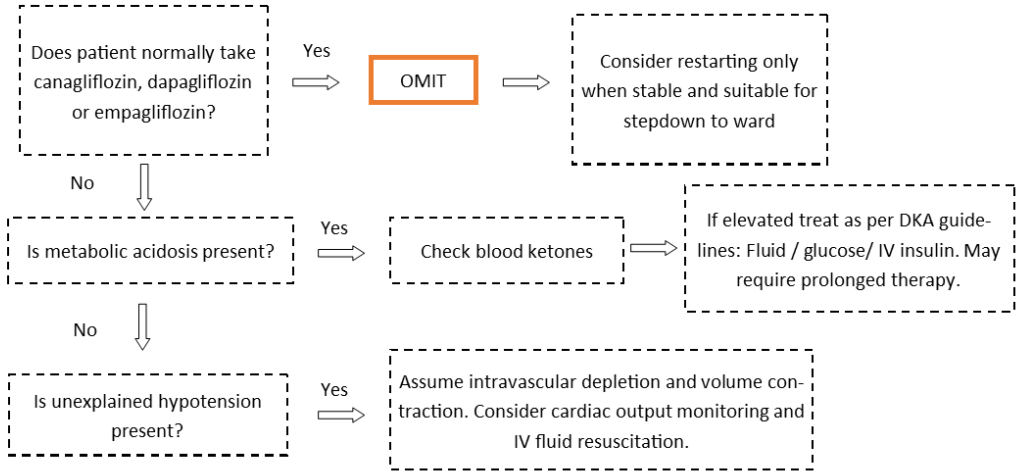
- SGLT-2 inhibitors reduce the renal reabsorption of glucose and are associated with an osmotic diuresis which may cause profound hypovolaemia

- They are associated with a euglycaemic ketoacidosis that may exist for several days after discontinuation of treatment. This a particular risk to critically ill patients. 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. Treatment of this condition should involve following the trust guidelines on Diabetic Ketoacidosis. It involves fluid resuscitation with careful supply of IV dextrose and saline along with intravenous insulin. Ketones should be monitored for 48-72 hours after treatment has been suspended

- 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

Canagliflozin, Dapagliflozin & Empagliflozin

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors: *Reversibly inhibit sodium-glucose co-transporter 2 in the renal proximal convoluted tubule to reduce glucose re-absorption and increase urinary glucose excretion.*



SGLT-2 inhibitors cause an osmotic diuresis through renal glucose losses which may be associated with hypovolaemia and intravascular volume depletion particularly in critically ill patients.

May be associated with euglycaemic diabetic ketoacidosis, check blood ketones on admission if patient has been an SGLT-2 inhibitor. The renal effects of these drugs may last a few days after they are stopped.

Patients should have their SGLT-2 inhibitors held for a minimum of 72 hours preoperatively.

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 6 mmol/l in a patient who has been taking sulphonylureas prior to admission to critical care, consider starting a background glucose infusion until full feed is established to minimise the risk of a hypoglycaemia

- Sulphonylureas 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. They may be considered in certain patients with Type 2 Diabetes e.g. prolonged ventilatory wean with single organ support

Meglitinides

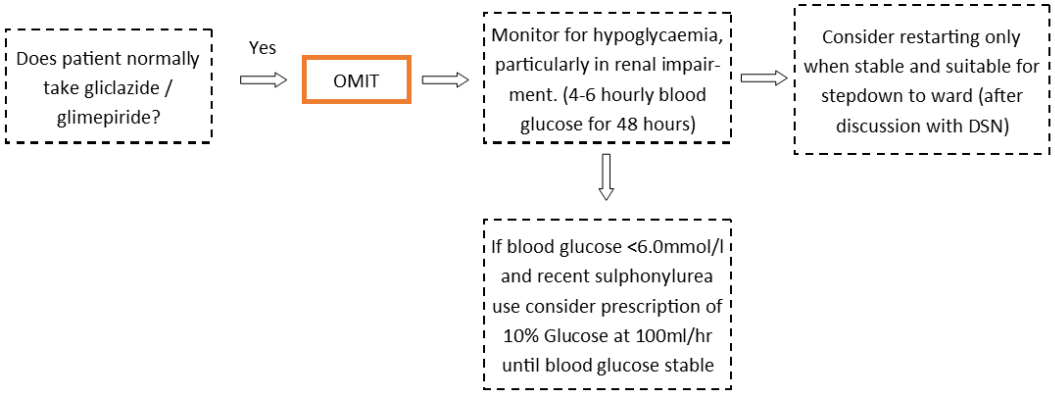
- Repaglinide, nateglinide and mitiglinide act in a similar manner to the sulphonylureas (bind to beta cells causing insulin release). They are less potent and have a shorter duration of action than sulphonylureas but still may pose a risk of hypoglycaemia

- Repaglinide, nateglinide and mitiglinide 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, is eating or has enteral route established and has been reviewed by the Diabetes Specialist nurse. They may be considered in certain patients with Type 2 Diabetes e.g. prolonged ventilatory wean with single organ support

Gliclazide/ Glimepiride

Sulphonylureas: *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.

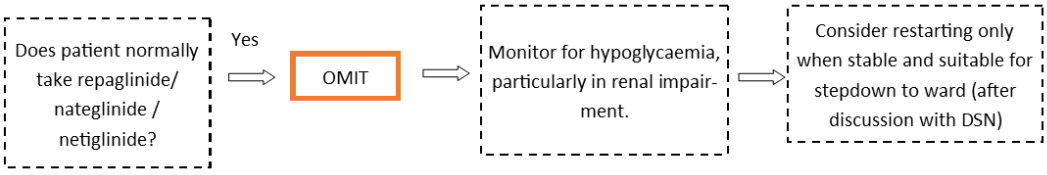
Multiple drug interactions

Omit whilst in critical care

There may be a role for using gliclazides in Critical Care patients who are weaning from critical illness e.g. prolonged respiratory wean or in patient's with spinal cord injuries who require long term ventilation. They may aid in reducing the need for a VRII, basal insulin and decrease glucose variability. They should only be started after discussion with the Diabetes Specialist Nurse.

Repaglinide/ Nateglinide / Metiglinide

Meglitinides: *bind to receptors on Beta cells causing increased release of insulin*



Shorter acting and less potent than sulphonylureas but may still cause significant hypoglycaemia.

Omit whilst in critical care

There may be a role for using meglitinides in Critical Care patients who are weaning from critical illness e.g. prolonged respiratory wean or in patient's with spinal cord injuries who require long term ventilation. They may aid in reducing the need for a VRII, basal insulin and decrease glucose variability. They should only be started after discussion with the Diabetes Specialist Nurse.

Thiazolidinediones

- Pioglitazone and rosiglitazone 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 and in chronic use associated with peripheral oedema, fluid retention and exacerbation of congestive cardiac failure

- Pioglitazone and rosiglitazone 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

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

Pioglitazone / Rosiglitazome

Thiazolidinediones*: bind to nuclear receptors increasing uptake into adipocytes of free fatty acids therefore increasing glucose metabolism*

Can cause marked 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

Acarbose

Alpha-glucosidase inhibitors: *intestinal brush border enzyme inhibitor*

Likely to cause GI disturbance and diarrhoea.

Omit whilst in critical care

Hypoglycaemia

Appendix C: see Hypoglycaemia algorithm

- Avoidance of hypoglycaemia is a key 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 the effect may be related to the severity of the hypoglycaemia

- 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 a 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

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 – 10 mmol/l for 2 consecutive hours this may be extended to 2 hourly checks

- 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 6.0 mmol/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 < 4.0 mmol/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

- Minimising interruptions to glucose supply and avoidance of unopposed insulin are essential. Any patient receiving enteral feed which is interrupted either deliberately (e.g. for procedures) or unintentionally due to tube displacement should be considered for a replacement glucose supply

- 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 replacement fluid should be at the discretion of the caring physician and may 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. Regular review of fluids and insulin should prompt the caring team to ask whether IV insulin is necessary

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 – "**Four is the Floor"**

    - 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***

- As a part of religious obligation Muslim patients who are fasting may refuse treatment. It is permissible within the Islamic religion to break the fast if there is a risk to life. As fasting is a mandatory obligation within Islamic faith, however, there are conditions when fasting becomes non-mandatory and diabetes is among one of those conditions.

  Staff are reminded to ensure the religious and non-religious needs of all patients

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

Rationale & Supporting Evidence

Monitoring of blood glucose levels

Monitoring of blood glucose in ICU can be done via several available devices. Sampling time must be minimised with readily available results, particularly during close monitoring when the patient is on an insulin infusion. Laboratory blood glucose remains the reference standard but has the disadvantages of requiring a relatively large volume of sampled blood and incorporates unacceptable delays in obtaining results for use in calculating insulin infusion dosage changes. Arterial blood analysers are of an acceptable equivalent accuracy to the laboratory standard. Point of Care (POC) analysers have an acceptable level of accuracy in the stable patient but their accuracy is diminished in critically ill patients and at the extremes of measurement.[1,2] There have been reports of inadvertent insulin administration resulting from sampling from flush lines contaminated with glucose containing fluids in critical care units.[3] Recent consensus guidelines recommend the use of arterial blood gas analysers as reliable but potentially costly method of intermittent glucose monitoring.[4]

Target blood glucose range

There have been a number of studies and consensus guidelines with various target ranges for glucose control in Critical Care. Following the Leuwen studies in the early 2000's our unit has used a tight glycaemic control policy (4.0 – 6.7 mmol/l) with the use of a computer algorithm. The publication of the NICE-SUGAR trial in 2009 and subsequent other studies have shown either no benefit or harm associatedfrom tight glucose control. Concensus guidelines[5] from the Critical Care Society in 2012 advocate commencing treatment for hyperglycaemia above 8.3mmol/l but absolutely above 10.0mmol/l. The "Conventional" arm of the NICE-SUGAR trial used a treatment threshold above 10.0mmol/l with a target range of 7.8-10mmol/l. This is line with UK

NHS Perioperative Guidelines[6] (specify 4-10mmol/l but state 6-10mmol/l also acceptable) and the Joint British Societies Guidelines for Inpatient Diabetes Care, 2014[7] (6-10mmol/l).

Individualised Target Ranges

Whilst it is not clear what the ideal target range for glucose is in criticaly ill patients it is apparent that an individualised strategy may be beneficial. An international cohort study by Krinsley et al[8] demonstated that the presence of diabetes modified the normal risks associated with hyperglycaemia, hypoglycaemia and glucose variability and suggested that a higher target range for glucose may be beneficial in those with diabetes.[9] A higher treatment threshold (>14mmol/l) and target range (10-14mmol/l) in those with preexisting diabetes has been shown to be safe in an exploratory analysis and cohort study, may reduce glucose variability, hypoglycaemia and insulin requirments. The LUCID Trial, currently recruiting in Australasia will provide further evidence on this question. Pending the results of this study our guidelines will recommend targetting a range reflecting the Conventional Arm of the NICE-SUGAR trial.

Neurological Injury

There remains conflicting evidence regarding ideal target strategy in patients with neurological injury. Hyperglycaemia is associated with a worse prognosis in a variety of patients with neurological injury. Treatment with intensive insulin therapy is however associated with an increased risk of hypoglycaemia.[10] Microdialysis catheter placement in areas of injured brain in traumatic brain injury has demonstrated low levels of diasylate glucose suggesting energy crisis in patients treated with insulin to control hyperglycaemia.[11] Hyperglycaemia as a stress response may be particularly important in brain injured patients as brain metabolism is glucose dependent. The optimal glucose target is yet to be defined but the avoidance of hypoglycaemia is of paramount importance.

Insulin infusion – variable rate versus dynamic sliding scale via computer algorithm

Current trust protocol for inpatient insulin infusion is via Variable Rate Insulin Infusion (VRII). This has the disadvantage of having a self defined target blood glucose range of 4.0-7.0mmol/l, a level lower than desired. VRII's do not take into account the trend in glucose over time and are therefore at more risk of rapid changes and increased glucose variability. A Dynamic Sliding Scale reduces this potential hazard and

although this is more intensive in terms of nursing workload. The algorithm used in the control arm of the NICE- SUGAR trial ich targets the desired range of 7.8-10.0mmol/l is readily available online and can be converted into an simple to use tool via an Excel workbook or online tool.

Basal Insulin, Oral and Novel Antidiabetic Agents

The increasing prevalence of Type 2 Diabetes and the explosion of medications licenced to treat this condition mean that an increasing number of our critically ill patients will present whilst taking these medications. Intravenous insulin infusions have an inherent risk of hypoglycaemia which may be mitigated by the continuation or addition of alternative antidiabetic agents. These agents may have specific risks and benefits in the critically ill patient.

Basal / Long acting Insulin

Continuation or addition of a long acting insulin may reduce intravenous requirements and glucose variability on a variable rate infusion. There are few studies examining subcutaneous insulin absorption in critically ill patients. Insulin has been shown to have poor absorption in non-critically ill patients with tissue oedema. Absorption of subcutaneous low molecular weight heparin is impaired in patients on vasopressors, suggesting a risk of similar problems with insulin.[12] Injection site may affect absorption with injection into areas of lipohypertrophy, oedema and inflammation likely to affect absorption. Where oedema is widespread and dependent the upper arm may be preferable to the abdomen.

Metformin

Metformin is contraindicated in patients with severe hepatic, renal and cardiovascular failure. This is due to the perceived risk of lactic acidosis associated with biguanide medications. A Cochrane review of the incidence of lactic acidosis in 2009 however found no evidence of metformin induced lactic acidosis and found the incidence of lactic acidosis to be lower in the Type 2 diabetic population taking metformin than in those not taking metformin.[13] Recent cohort studies have found that metformin use at admission to critical care was associated with an improved 30-day mortality, particularly in those patients that continued metformin in the early phase of their admission[14] and in the second study[15] was found to be associated with a lower mortality in sepsis patients, with no evidence of harm overall.

Given the low-quality evidence, and until high quality studies on the subject are available it would be sensible to advise that metformin is suspended on admission to ICU if any of the above contraindications are present. Given the potential benefits of increased insulin sensitivity, decreased glucose variability associated with higher insulin infusion rates and the perceived benefits of immunomodulation and cardiac protective effects, it would be reasonable to restart or even start this in those patients who are on established enteral feed and in whom renal failure has been excluded.

Glucose-like-peptide (GLP) 1 Analogues

A few small, low grade quality trials have demonstrated use of the incretin mimetics liraglutide[16] and exenatide[17] in critically ill patients with hyperglycaemia to be effective and with a lower rate of hypoglycaemia than insulin infusions. The main side effects of these therapies were noted to be nausea and vomiting. An intrinsic effect of these agents is to delay gastric emptying which may exacerbate poor gastric absorption in the critically ill. As administration is via the sub-cutaneous route, absorption is likely to be affected in patients on high dose vasopressors and with widespread oedema. Whilst there is growing evidence that these agents may be safe and effective in reducing critical illness induced hyperglycaemia whilst reducing hypoglycaemia and glucose variability, there is a lack of high-quality studies to support routine use in the critically ill patient.[18] However, it is reasonable to continue administration in those without clear contraindications.

Dipeptidyl peptidase-4 (DPP-4) inhibitors.

Sitagliptin and Linagliptin are oral agents that stimulate incretin release and suppress 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. They should be discontinued in patients with high gastric aspirates, nausea or vomiting.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

SGLT-2 inhibitors reduce the renal reabsorption of glucose and may be associated with reduced cardiovascular complications in patients with Type 2 diabetes[19] and improved HBA1c in patients with Type 1 diabetes[20]. They are likely to become more common in patients presenting to critical care. Due to their class mechanism of action they may exacerbate hypovolaemia in the acutely unwell patient due to an osmotic

diuretic effect and have been associated with severe hypovolaemia. A report by the European Medicines Agency concluded that SGLT-2 inhibitors caused an increased risk of potentially fatal euglycaemic ketoacidosis. SGLT-2 inhibitors should therefore be withheld in[21] patients undergoing major surgery or in those with acute illness. They should not be restarted in critical care but may be considered when a patient is stable, on full enteral feed and considered well enough to step down to ward care.

Hypoglycaemia

Hypoglycaemia is a common side effect of insulin therapy in the ICU. Various studies have demonstrated an association between episodes of hypoglycaemia and worse outcomes in critically ill patients. A post -hoc analysis of the NICE-SUGAR trial demonstrated a doubling of the risk of mortality in patients with one episode of severe hypoglycaemia (<2.3mmol/l) with an apparent dose-response relationship in harm.[22] Risk factors for hypoglycaemia in the ICU include intensive insulin therapy (versus liberal), history of diabetes, mechanical ventilation, continuous veno-venous haemofiltration and ICU length of stay.[23]

2. Equality Impact Assessment.

EQIA registration Number: 2019-155

3. Consultation, Approval and Ratification Process

Critical Care Diabetes Working Group devised guideline.

Consultation with all unit medical, nursing and pharmacy leadership.

Approval and ratification at Critical Care Board.

Unit Q and S leads and clinical director, group clinical director, unit matrons and practice educators, pharmacy team will be responsible for clinical roll out and monitoring.

Incident reporting of adverse events reported e.g. hypoglycaemia will be audited and reviewed at unit and board Q and S meetings.

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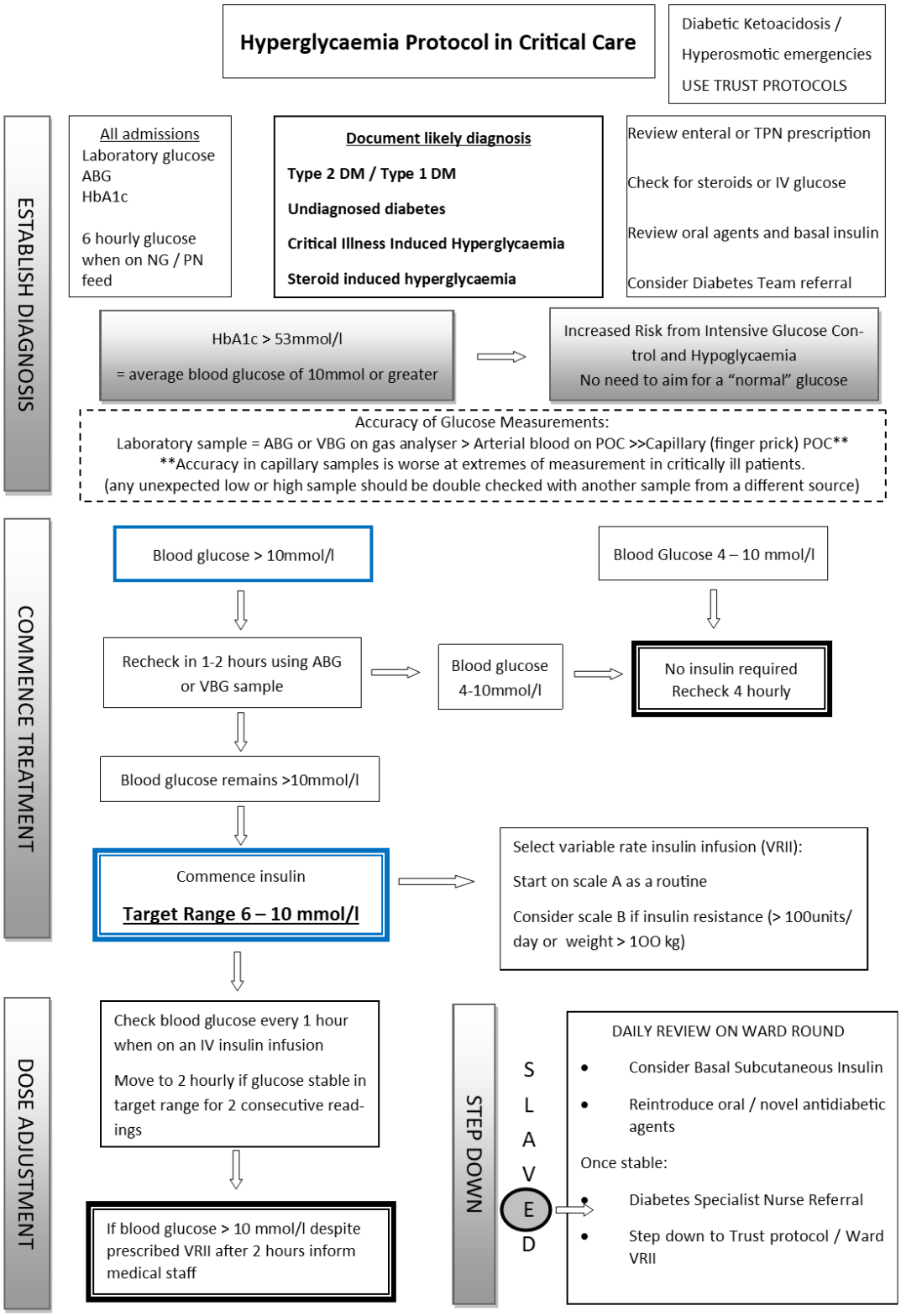
Appendix 1:


Hyperglycaemia Protocol in Critical Care
Diabetic Ketoacidosis / Hyperosmotic emergencies USE TRUST PROTOCOLS
ESTABLISH DIAGNOSIS
All admissions
Laboratory glucose
ABG
HbA1c
6 hourly glucose when on NG / PN feed
Document likely diagnosis
Type 2 DM / Type 1 DM
Undiagnosed diabetes
Critical Illness Induced Hyperglycaemia
Steroid induced hyperglycaemia
Review enteral or TPN prescription
Check for steroids or IV glucose
Review oral agents and basal insulin
Consider Diabetes Team referral
HbA1c > 53mmol/l
= average blood glucose of 10mmol or greater
Increased Risk from Intensive Glucose Control and Hypoglycaemia
No need to aim for a "normal" glucose
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
Blood glucose > 10mmol/l
Blood Glucose 4 – 10 mmol/l
Recheck in 1-2 hours using ABG or VBG sample
Blood glucose 4-10mmol/l
No insulin required
Recheck 4 hourly
Blood glucose remains >10mmol/l
Commence insulin
Target Range 6 – 10 mmol/l
Select variable rate insulin infusion (VRII):
Start on scale A as a routine
Consider scale B if insulin resistance (> 100units/ day or weight > 1OO kg)
DOSE ADJUSTMENT
Check blood glucose every 1 hour when on an IV insulin infusion
Move to 2 hourly if glucose stable in target range for 2 consecutive readings
If blood glucose > 10 mmol/l despite prescribed VRII after 2 hours inform medical staff
STEP DOWN
S L A V E D
DAILY REVIEW ON WARD ROUND
Consider Basal Subcutaneous Insulin
Reintroduce oral / novel antidiabetic agents
Once stable:
Diabetes Specialist Nurse Referral
Step down to Trust protocol / Ward VRII

Appendix 2:

Variable Rate Insulin Infusion (VRII)

- Record blood glucose, insulin rate and scale used on critical care chart/CIS
- Recheck blood glucose according to guideline
- ***Ensure there is never unopposed insulin infusion if blood glucose < 12 mmol/l. The following are acceptable:***

  Enteral (>10ml/hr) or parenteral nutrition is running

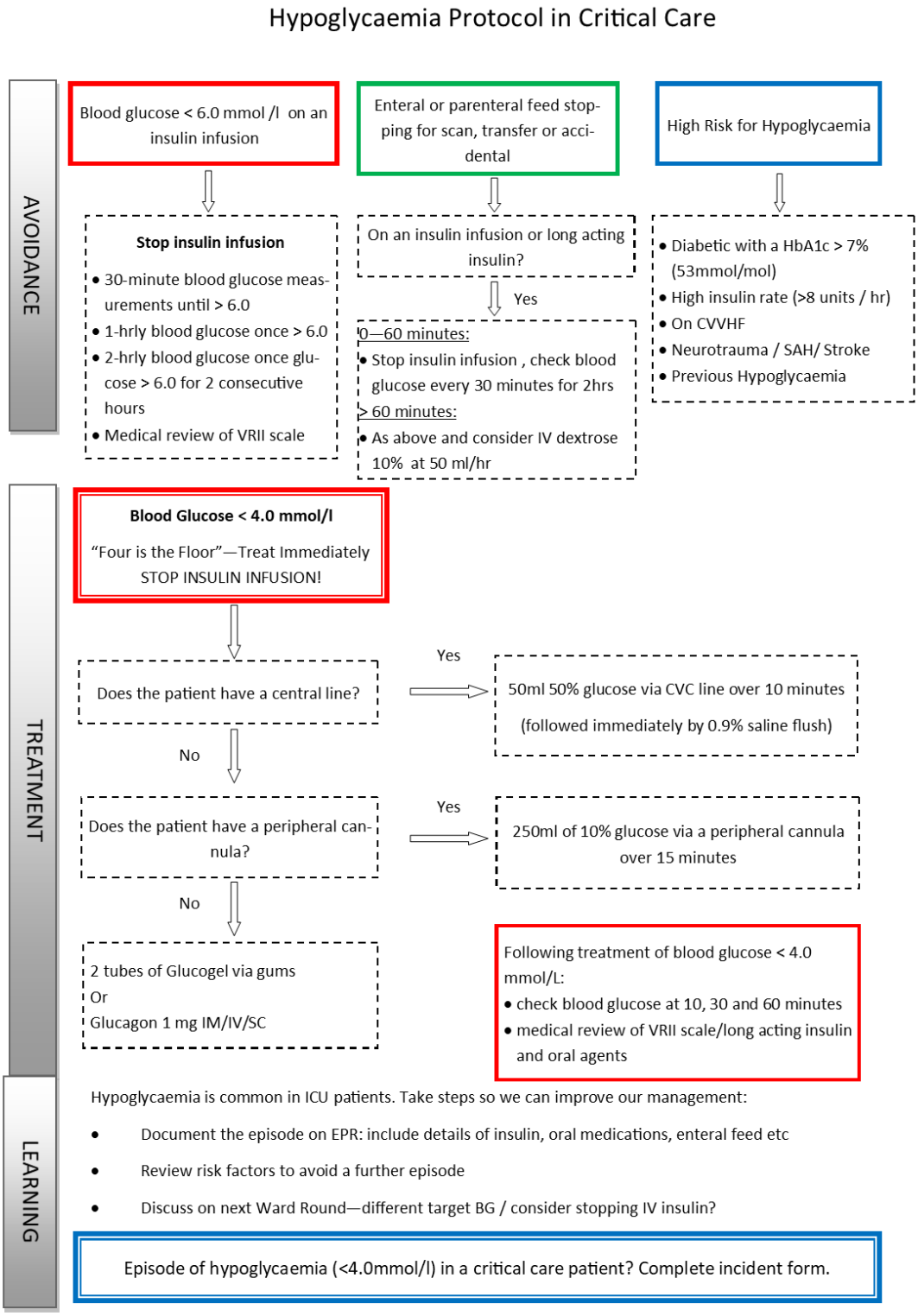
  0.45 % NaCL/5% glucose +/- KCL—42mlhr or 83ml/hr

  IV 10% glucose—25ml/hr or 50ml/hr

  5% dextrose—50ml/hr or 100ml/hr
- Aim to start all patients on the standard scale A
- Scale B may be selected from the start e.g. patient requiring > 100units insulin/day, weight > 100kg
- If blood glucose > 10 mmol/l for more than 2 hours on Standard scale A inform medical staff and consider moving to Scale B
- Any episode of blood glucose < 6.0mmol/l on Scale B move back to Scale A
- Scale C is a bespoke scale to be used if there is insulin resistance and persistently elevated blood glucose on Scale B or if the patient is insulin sensitive (e.g. requiring < 24 units/day) on Scale A

Blood Glucose (mmol/l)	**Scale A (= Standard Scale) Units of insulin/hr**	**Scale B (= Increased Rate Scale) Units of insulin/hr**	**Scale C (= Bespoke Scale) Units of insulin/hr**
< 4.0	0 Treat Hypoglycaemia	0 Treat Hypoglycaemia	0 Treat Hypoglycaemia
4.1—6.0	0	0	.....
6.1—8.0	1	2	.....
8.1—12.0	2	4	.....
12.1-15.0	4	6	.....
15.1-17.0	8	10	.....
> 17.1	10	12	.....
Dr's signature: **Date and Time:**	....	....	....

Appendix 3:


Hypoglycaemia Protocol in Critical Care
AVOIDANCE
Blood glucose < 6.0 mmol /l on an insulin infusion
Enteral or parenteral feed stopping for scan, transfer or accidental
High Risk for Hypoglycaemia
Stop insulin infusion
• 30-minute blood glucose measurements until > 6.0
• 1-hrly blood glucose once > 6.0
• 2-hrly blood glucose once glucose > 6.0 for 2 consecutive hours
• Medical review of VRII scale
On an insulin infusion or long acting insulin?
Yes
0—60 minutes:
• Stop insulin infusion , check blood glucose every 30 minutes for 2hrs
> 60 minutes:
• As above and consider IV dextrose 10% at 50 ml/hr
• Diabetic with a HbA1c > 7% (53mmol/mol)
• High insulin rate (>8 units / hr)
• On CVVHF
• Neurotrauma / SAH/ Stroke
• Previous Hypoglycaemia
TREATMENT
Blood Glucose < 4.0 mmol/l
"Four is the Floor"—Treat Immediately
STOP INSULIN INFUSION!
Does the patient have a central line?
Yes
50ml 50% glucose via CVC line over 10 minutes
(followed immediately by 0.9% saline flush)
No
Does the patient have a peripheral cannula?
Yes
250ml of 10% glucose via a peripheral cannula over 15 minutes
No
2 tubes of Glucogel via gums
Or
Glucagon 1 mg IM/IV/SC
Following treatment of blood glucose < 4.0 mmol/L:
• check blood glucose at 10, 30 and 60 minutes
• medical review of VRII scale/long acting insulin and oral agents
LEARNING
Hypoglycaemia is common in ICU patients. Take steps so we can improve our management:
• Document the episode on EPR: include details of insulin, oral medications, enteral feed etc
• Review risk factors to avoid a further episode
• Discuss on next Ward Round—different target BG / consider stopping IV insulin?
Episode of hypoglycaemia (<4.0mmol/l) in a critical care patient? Complete incident form.