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For healthcare professionals and carers working in primary care and the community:

# MANAGING DIABETES DURING INTERCURRENT ILLNESS



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# **RATIONALE AND REMIT**

This document was developed in 2012 to provide information and guidance on the community management of diabetes in adults during episodes of illness. It is intended to serve as a helpful resource for a range of people who support individuals with diabetes, including medical professionals (e.g. nurses, GPs) and non-medical professionals (e.g. those working in residential care, in community nursing teams, prisons, young offender institutes).

The recommendations have been reviewed and updated to produce this 2nd edition by Training, Research and Education for Nurses in Diabetes (TREND-UK). We are grateful for the contribution and support from the original authors and organisations.

When implementing any advice in the document, full account should be taken of the local context and any action taken should be in line with statutory obligations required of the organisation and individual. No part of the publication should be interpreted in a way that would knowingly put anybody at risk.



# INTRODUCTION: THE CHALLENGE OF MANAGING DIABETES DURING INTERCURRENT ILLNESS

Although people with diabetes do not necessarily become ill more often than individuals without diabetes, they do have higher rates for infections especially bone and joint infections, sepsis and cellulitis (Carey et al, 2018).

Depending on the type of diabetes they have, the type of illness and the diabetes treatment they are using, the blood glucose levels of individuals may respond differently to illness. For example, an episode of vomiting and diarrhoea disrupts normal eating, appetite and digestion so blood glucose levels may drop and lead to hypoglycaemia. However, the stress hormones produced by the body to fight an infection (adrenaline and cortisol) reduces the body's sensitivity to the effects of insulin (insulin resistance). This will cause a rise in blood glucose levels to provide the energy required for the body's response, even if the individual is not eating. In an individual without diabetes, insulin production is increased by the pancreas to utilise this glucose. Someone with diabetes may be unable to do this effectively, resulting in hyperglycaemia (high blood glucose).

Examples of illnesses which may cause hyperglycaemia include:

- The common cold
- Influenza
- Urinary tract infection
- Chest infection
- Abscess
- Injury such as a fracture



Mismanagement of diabetes during periods of illness can lead to other problems such as dehydration or the development of serious acute diabetes complications. Implementation of the correct advice can reduce the risk of this occurring. Ideally, all people with diabetes should receive structured education on how to self-manage the condition, including what to do during episodes of intercurrent illness.





# ACUTE DIABETES COMPLICATIONS

Stress and infection cause a rise in adrenaline and cortisol which leads to insulin resistance. This reduces the effectiveness of insulin in enabling the body to utilise glucose as energy. It also results in a rise in the counter-regulatory hormone glucagon which causes glycogenolysis (break down of hepatic glycogen stores) and gluconeogenesis (production of glucose from other substances) by the liver. In someone with diabetes, blood glucose levels may rise leading to an osmotic diuresis (excess urination) leading to dehydration. Dehydration itself causes further insulin resistance (French et al, 2019).

Without correct management, this situation can lead to the development of severe acute complications of Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycaemic State (HHS). These conditions are medical emergencies and require urgent hospitalisation. A brief description of both is given below to enable readers to recognise and understand the complications, **not** to suggest they can be managed in the community.

#### Diabetic ketoacidosis (DKA):

DKA occurs as a consequence of absolute or relative insulin deficiency resulting in insufficient glucose needed for energy to be able to enter into cells. It consists of ketonaemia (ketones in the blood which are produced in response to the body being unable to use glucose for energy adequately), hyperglycaemia and acidaemia where the blood becomes more acidic due to the rise in the ketone level. Changes in the pH of the blood disrupts many processes in the body needed for life. Although commonly associated with type 1 diabetes, occasionally people with type 2 diabetes can also develop DKA. Before the discovery of insulin nearly 100 years ago, DKA was a fatal condition. With improved understanding and treatment, mortality rates for DKA have fallen significantly in the last 20 years to less than 1%, although for very elderly people or those with several co-morbidities, this is about 5% (French et al, 2019).

#### Diagnosis of DKA:

Blood ketones 3mmol/L or greater (or more than 2+ on urine ketone strips)

Blood glucose higher than 11 mmol/L

Bicarbonate less than 15 mmol/L and/or venous pH less than 7.3  $\,$ 

#### (JBDS-IPCG, 2013)

#### Signs and symptoms of DKA:

#### A These develop rapidly (over a few hours)



Diabetic ketoacidosis can be triggered by (French et al, 2019):

- Illness particularly infections like pneumonia and urinary tract infections (about 45% of cases)
- Insulin omission or inadequate amounts (about 20% of cases)
- Physical or emotional trauma
- Heart attack
- Alcohol or drug abuse
- Certain medications such as corticosteroids or SGLT2 inhibitors

Individuals who may be at particular risk of developing DKA (Mayo, 2019):

- Those with type 1 diabetes
- Those who frequently miss insulin injections
- Treatment with SGLT2 inhibitors or atypical antipsychotics
- Treatment with GLP-1 Receptor Agonist injections when concomitant insulin is reduced too quickly or stopped
- A DKA is a medical emergency. The individual needs hospitalisation for rehydration, restoration of electrolyte balance, and insulin therapy

#### Hyperosmolar hyperglycaemic state (HHS):

HHS differs from DKA in that it has a slow onset (developing over days or weeks) resulting in a more severe degree of dehydration. Extremely high blood glucose levels (often over 30 mmol/L) and high serum osmolality are features but there is a lack of significant amount of blood ketones (less than 3 mmol/L) (JBDS-ICG, 2012).





Like DKA, the most common precipitating factors are infection and inadequate insulin therapy. Certain drugs like steroids and excess diuretics can also predispose to severe hyperglycaemia and HHS. The mortality rate for HHS is higher than DKA (about 10 - 20%) as it tends to affect older people with type 2 diabetes and multiple underlying co-morbidities (French et al, 2019). It is complicated by vascular complications such as heart attacks, strokes and peripheral arterial thrombosis, and seizures and cerebral oedema (swelling of the brain) (JBDS-ICG, 2012).

▲ HHS is a medical emergency. The individual needs hospitalisation for rehydration, anti-coagulation therapy and restoration of electrolyte balance. Despite the very high blood glucose level on admission, the individual may not require insulin therapy.

### GENERAL PRINCIPLES OF MANAGING DIABETES DURING INTERCURRENT ILLNESS

The aim of management is to maintain reasonable blood glucose levels (avoiding both hypoglycaemia and hyperglycaemia) and prevent severe dehydration and progression to DKA or HHS. The management of blood glucose levels during a period of intercurrent illness will depend on the type of diabetes, the type of illness and the anti-hyperglycaemic treatment the individual has.

Rest: avoid strenuous exercise.

**Fluids:** to avoid dehydration, the individual should drink plenty of sugar-free fluids. These should be sipped gently throughout the day, especially if nauseated (at least 100 ml per hour), aiming for at least 2 ½ to 3 ½ litres (4 to 6 pints) over 24 hours.

**Meal replacements:** Being ill, especially if febrile with an infection, consumes calories. If the individual is unable to eat usual meals, calories should be replaced by easily digested carbohydrate (starchy or sugary) foods and drinks. The table below gives some suggestions. Each item is equivalent to about 10 gram of carbohydrate (e.g. equivalent to an egg-sized potato, thin slice of bread, or a tablespoon of cooked rice or pasta).

Food or drink		Quantity
	Fruit juice	100 ml
	Milk	200 ml
	lce-cream	1 large scoop
	Tomato soup	½ large tin (200 gram)
2	Yoghurt	Small 150 gram pot
	Rich tea or malted milk biscuits	2

**Treat the illness/symptoms:** Over-the-counter painkillers and cough syrups can be used to relieve high temperature, sore throat and cough. These do not have to be sugar-free varieties as they contain very little glucose and are taken in small quantities. The individual should see their GP if an infection is suspected as antibiotics may be required.

Monitoring blood glucose levels: As mentioned in the introduction to this document, blood glucose levels vary in response to illness depending on the type of illness, the type of diabetes the individual has, and the type of glucose-lowering treatment he or she uses to manage their diabetes. Regular monitoring, ideally using blood glucose testing equipment rather than urine testing strips, is essential to guide the appropriate management of diabetes, especially if adjusting insulin dose. People using insulin should test their blood glucose levels at least every 4 to 6 hours including during the night when unwell. Individuals with type 1 diabetes with blood ketone levels of 1.5 mmol/L or greater should test every 2 hours including during the night and give additional doses of insulin until ketone levels reduce (see insulin adjustment section).

Some individuals monitor their glycaemic status with Continuous Glucose Monitors or Flash glucose monitors. In situations where the blood glucose levels may be fluctuating rapidly, these devices may not be reliable. Before administering extra insulin, a capillary finger-prick blood glucose reading should be taken to confirm hyperglycaemia.

**Monitoring blood ketone levels:** People with type 1 diabetes should have access to blood ketone testing equipment and be taught how to interpret and respond appropriately to the results (NICE 2015a). Generally, people who have type 2 diabetes are not routinely prescribed ketone-testing equipment as the risk of DKA is lower in this type of diabetes.

Although urine ketone testing strips are less costly and simpler to use, they are not recommended. They do not detect B-hydroxybutyrate which is the predominant metabolite in DKA. Also, urine output is low in people who are dehydrated so it may be difficult to monitor progress of treatment as samples may be infrequent (Dhatariya K, 2016).

A However, any person with diabetes (either type 1 or type 2 diabetes) who is acutely unwell should have their blood ketone levels checked, especially if they are vomiting.

#### Interpreting blood ketone levels:

Less than 0.6 mmol/L	Normal
0.6 to 1.5 mmol/L	Risk of developing DKA. Retest in 2 hours
1.6 to 2.9 mmol/L	High risk of developing DKA. Increase in insulin required
3 mmol/L or higher	Very high risk of DKA. Needs urgent medical attention and may need admission to Accident and Emergency department

# ADJUSTMENT OF GLUCOSE-LOWERING MEDICATIONS

Increasing the frequency of monitoring blood glucose levels will support the appropriate adjustment of glucoselowering medications. In most cases, these medications should be continued (but see the next section) even if appetite is poor. Sulphonylureas and insulin doses may need to be reduced temporarily if blood glucose levels are dropping lower than the agreed target. Typically however, adults with acute intercurrent illness are at risk of worsening hyperglycaemia and so these treatments will need to be increased if levels are consistently above target. Insulin may be required temporarily in people with type 2 diabetes until the intercurrent illness has resolved (NICE 2015b).

# Type 1 diabetes - Adjusting insulin during intercurrent illness:

If blood glucose levels are lower than the agreed target, insulin doses may need to be reduced by 10 to 20% and mealtime insulin doses may be omitted if little or no carbohydrate is consumed. **However, insulin must never be stopped completely in someone with type 1 diabetes.** 

If blood glucose levels are above the agreed target, insulin doses will need to be increased. The presence of blood ketones reduces the body's sensitivity to the action of insulin so injected insulin requirements significantly increase even if the individual is not eating. The degree of ketonaemia determines the frequency of monitoring and additional insulin boluses, and the amount of insulin required. The algorithms below suggest the process for someone with type 1 diabetes to follow if they have hyperglycaemia with less than 1.5 mmol/L of ketones, and the process to follow if they have ketones 1.5 mmol/L or greater.





Managing your insulin dose when your blood ketones are less than 1.5 mmol/L

If you start vomiting, are unable to keep fluids down, or are unable to control your blood glucose or ketone levels, you must seek urgent medical advice. DON'T STOP TAKING YOUR INSULIN EVEN IF YOU ARE UNABLE TO EAT

# Managing your insulin dose when your blood ketones are 1.5 mmol/L or higher



your blood glucose or ketone levels, you must seek urgent medical advid DON'T STOP TAKING YOUR INSULIN EVEN IF YOU ARE UNABLE TO EAT

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#### Insulin pump devices:

Insulin pumps use quick-acting insulin to provide a continuous background of insulin delivery, with additional boluses of insulin calculated by the user and given when carbohydrate is consumed. As insulin pump users do not use any long-acting basal insulin, they can rapidly develop DKA if the pump has a malfunction or the insulin delivery is interrupted (e.g. the tubing has become kinked or the cannula is dislodged). Pump users are trained to use a fast, aggressive and methodical approach to manage raised blood glucose levels to prevent the development of significant ketone levels. This involves setting a temporary increased basal rate and giving correction doses of guick-acting insulin using a pen device. The rationale for using a pen device is because the insulin pump calculates how much insulin is in circulation and may not deliver the frequent extra insulin doses required. Details of pump use is beyond the scope of this document as individuals using insulin pumps should be supported by a diabetes specialist team.

# Type 2 diabetes - Adjusting insulin during intercurrent illness:

If the blood glucose level is persistently greater than 11 mmol/L, the insulin dose needs to be increased as follows:

11.1 to 17 mmol/L	Add 2 extra units to each dose
17.1 to 22 mmol/L	Add 4 extra units to each dose
Over 22 mmol/L	Add 6 extra units to each dose

If the individual usually takes more than 50 units in total daily, these adjustments should be doubled. All adjustments are incremental and should be reduced gradually as the illness resolves.

If the blood glucose levels are dropping down to 4 mmol/L or less, the usual insulin dose should be reduced by 10% (e.g. if the dose is usually 20 units, reduce by 2 units to 18 units. If it is usually 40 units, reduce by 4 units to 36 units). Ensure the individual or their carer knows how to recognise and treat hypoglycaemia and has "hypo" treatments available.





### SPECIFIC ADVICE ABOUT COMMONLY USED DIABETES MEDICATIONS

The following section outlines the advice provided in the Product Specific Characteristics information and other sources for a number of medications commonly taken by people with diabetes during periods of intercurrent illness.

#### Metformin:

Metformin, in the presence of dehydration and acute reduction in renal function, accumulates and increases the risk of developing a very rare condition called lactic acidosis. In cases of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Metformin is contraindicated in people with eGFR <30 mL/ min and it should be temporarily discontinued in the presence of conditions that alter renal function. These include severe infection, shock and conditions which cause tissue hypoxia such as recent myocardial infarction.

www.medicines.org.uk/emc/product/594/smpc (accessed 8th August 2019)

#### Sulphonylureas:

Glibenclamide, Gliclazide, Glimepiride, Glipizide, Tolbutamide

Tablets in this class work by stimulating the beta cells in the pancreas to make more insulin, helping it to work more effectively (Diabetes UK)

These tablets can cause hypoglycaemia if taken without food so may need to be reduced if appetite is poor. However, they can be increased if the intercurrent illness is causing hyperglycaemia unless the individual is already taking the maximum dose.

#### Pioglitazone:

This medication reduces insulin resistance and improves sensitivity, allowing the insulin that the pancreas produces to work more effectively (Diabetes UK).

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. It should be discontinued if any deterioration in cardiac status occurs.

#### www.medicines.org.uk/emc/product/4730/smpc (accessed 8th August 2019)

#### DPP4-inhibitors (gliptins):

Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin

DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme that destroys the hormone incretin. Incretin hormones help the body to produce more insulin when needed and reduce the amount of glucose production when it's not needed (Diabetes UK).

The use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Individuals should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. DPP4-inhibitors and other potentially suspect medicinal products should be discontinued.

#### www.medicines.org.uk/emc/product/321/smpc (accessed 8th August 2019)



#### SGLT2 inhibitors:

#### Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively recent addition to the choice of oral glucoselowering medications. They work by inhibiting the reabsorption of glucose from the proximal tubule in the kidney and thus allowing the loss of glucose (and calories) in the urine. They can lower blood glucose levels and may also produce weight loss.

However, Diabetic Ketoacidosis has been reported in 4% per year of people with diabetes taking an SGLT2 inhibitor in certain circumstances. Originally licensed for people with type 2 diabetes only, increasingly people with type 1 diabetes may be prescribed them (Dapagliflozin included type 1 diabetes in its licence in 2019). The Association of British Clinical Diabetologists recommends the SGLT2 inhibitor should be discontinued in the following situations, to reduce the risk of developing DKA:

The SGLT2 inhibitor should be stopped:

- Ø if the individual is acutely ill
- Ø unable to eat
- Ø has nausea and vomiting and abdominal discomfort

People are especially at risk if:

- **A** following a low carbohydrate diet
- **A** during an episode of illness
- **A** are vomiting
- A have sustained an injury
- **A** experiencing starvation
- A have excessive alcohol consumption
- A have a significant reduction in insulin administration

#### (ABCD, 2019)

All people taking this medication should be given advice about the signs and symptoms of DKA. Interestingly, the blood glucose levels may not be significantly high in DKA associated with SGLT2 inhibitor (14 mmol/L or less), known as euglycaemic DKA, despite the individual being very unwell (French et al, 2019)

An increase in Fournier's gangrene (necrotising fasciitis of the perineum) has also been noted in men and women using SGLT2 inhibitors. This is a rare but serious lifethreatening condition requiring antibiotics and urgent surgical intervention. Individuals should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. The SGLT2 inhibitor should be discontinued. As uro-genital infection or perineal abscess may precede necrotizing fasciitis, these should be investigated promptly (GOV.UK, 2019a).

#### GLP-1 receptor agonists:

#### Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide

These non-insulin glucose-lowering injections for overweight people with type 2 diabetes mimic the action of a gut hormone and can lower blood glucose levels and may produce weight loss. Up until the end of May 2019, the MHRA's Yellow Card Scheme received 26 reports of diabetic ketoacidosis, and 10 reports of reactions relating to ketone body formation (increased blood ketones, ketonuria) in people taking Exenatide, Liraglutide, and Dulaglutide. These cases occurred in people who were also using insulin and where the insulin had either been inappropriately discontinued or the dose was significantly reduced. Nausea and vomiting are common side effects of GLP-1 receptor agonists but they are also well-known symptoms of DKA. The development of DKA should be considered in people who have recently begun using GLP-1 receptor agonist and whose insulin dose has been significantly reduced (GOV.UK, 2019b).

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Individuals should be informed of the characteristic symptoms of acute pancreatitis (acute abdominal pain, nausea and vomiting). If pancreatitis is suspected, the GLP-1 receptor agonist should be discontinued and seek urgent medical attention.

#### www.medicines.org.uk/emc/product/6585/smpc (accessed 8th August 2019)

#### Other medications:

Dehydration can be a significant risk to people taking certain medicines. These should be temporarily stopped if this occurs (Down S, 2018)

- A Diuretics: (e.g. furosemide or bendroflumethiazide) can cause dehydration or make dehydration more likely in an ill person.
- ACE Inhibitors (medicines ending in 'pril'), ARBs (medicines ending in 'sartan') and NSAIDs (e.g. ibuprofen or naproxen) may impair kidney function in people who are dehydrated which could lead to kidney failure



#### Corticosteroids:

**Corticosteroids** (also known as steroids) are hormones that occur naturally in the body. They can be artificially manufactured for a range of medicinal uses, such as reducing inflammation. They are available as tablets, injections, creams, ointments and inhalers. There are a number of different types of steroids and they vary in how long a single dose lasts (from approximately 8 hours to over 2 days). Steroids may be required either as a short course (5 days), a course that gradually reduces over a period of time or a continuous course for many years.

Steroids taken orally or by injection will cause a significant rise in blood glucose. This will require starting diabetes treatment, increasing the dose of existing glucose-lowering treatments, or changing from tablets to insulin to prevent the symptoms of hyperglycaemia, dehydration and the risk of HHS. Generally, the steroids should be continued and the hyperglycaemia addressed with treatment rather than discontinuing the steroids.

See Appendix 1 for more details on the management of diabetes and steroid treatment.. The TREND-UK patient leaflet on steroids can be accessed at: www.trend-uk.org/resources



# BEING PREPARED AND REDUCING RISK OF ACUTE COMPLICATIONS

Medications should be taken regularly as prescribed to maintain glycaemic targets. Poor glycaemic control reduces resistance to infection and slows healing rates.

- Encourage individuals to be prepared when going on holiday or as winter time approaches when illnesses like influenza are more common: advise to keep a sufficient supply of medication and insulin supplies and blood glucose monitoring strips, over-the-counter medications such as simple painkillers and cough syrup, and ketone strips if Type 1 diabetes. They should take advantage of recommended vaccinations/flu jab.
- Take the opportunity to revise information and check knowledge about what to do when ill (sick day rules) with the individual during the annual diabetes review. Give appropriate written information (www.trend-uk.org)
- Inform individuals at risk of DKA (particularly those with type 1 diabetes, and those taking SGLT2 inhibitors) about the signs and symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, excessive thirst, increased frequency of urination, difficulty breathing, confusion, unusual fatigue, or sleepiness) and the need for urgent medical attention if they occur.

When initiating an SGLT2 inhibitor or GLP-1 receptor agonist in those with type 2 diabetes, reduce concomitant insulin in a stepwise manner, and not too quickly or drastically.



## WHEN TO SEEK URGENT MEDICAL HELP

Seek urgent medical advice in the following situations:

- A In someone who is pregnant (DKA can be fatal to the unborn baby)
- ▲ Someone taking SGLT2 inhibitor who has the signs and symptoms of DKA even if the blood glucose level is normal or only slightly raised
- A If persistent vomiting and unable to keep fluids down
- A If blood ketones are 1.6 mmol/L or higher and the individual is unable to take appropriate action
- ▲ If unable to keep blood glucose levels above 3.5 mmol/L
- A If not improving or getting worse, despite following the advice described in this document



## SUMMARY



## **APPENDICES**

#### 1. Algorithm for Managing Glucose with Once Daily Steroid Therapy



#### If steroids are reduced or discontinued:

- A Review any changes made and consider reverting to previous therapy or doses
- If unsure at any stage about next steps or want specific advice on how to meet with patients needs or expectations please contact the Diabetes Specialist
  Team
- A If steroids are reduced and the individual is on a sulpholylurea agent or insulin there is a significant risk of hypoglycaemia . Please reduce the dose of these drugs in tandem with the steroid dose reduction

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   https:// www.verywellhealth.com/how-to-read-blood-ketone-test-results-3289640 (accessed 29th August 2019)

# **USEFUL RESOURCES:**

- Diabetes UK: www.diabetes.org.uk
- TREND-UK: www.trend-uk.org
- A range of useful leaflets for people with diabetes is available on the TREND-UK website
- Down S (2018) How to advise on sick day rules. Diabetes and Primary Care 20(1): 15-16
- ihub Medicines and Dehydration Patient Information: https://ihub.scot/media/1398/20180424-medicine-sick-day-rulespatient-leaflet-print-v20.pdf

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