Continuing Professional Development

CPD

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60 Second Summary

Diabetic ketoacidosis (DKA) is a medical emergency, typified by a triad of diagnostic criteria- acidosis (venous pH < 7.3 and/or serum bicarbonate < 15 mmol/L), ketosis (plasma ketones > 3.0 or significant ketonuria- +2 or more on standard ketone sticks) and hyperglycaemia (blood glucose levels >11.0 or known diabetes mellitus). It primarily occurs in type 1 diabetes mellitus (T1DM), usually precipitated by factors such as: non-compliance with insulin; intercurrent illness; surgery; with drugs such as corticosteroids, atypical antipsychotics, thiazide diuretics; or with alcohol or cocaine use. DKA is frequently the first presentation for new-onset diabetes. DKA can also occur in type 2 diabetes (T2DM), known as ketosis-prone T2DM. If not treated appropriately, DKA can be life-threatening and is the most common cause of diabetes-related death in younger diabetic patients (paediatric patients and young adults up to aged 25), usually due to a cerebral oedema, a serious complication. Management of paediatric DKA in Ireland is guided by a HSE National Clinical Guideline (2018) as well as a number of recent international guidelines- BPSED (British Paediatric Society of Endocrinology and Diabetes) 2020 and ISPAD (International Society for Paediatric and Adolescent Diabetes), 2018. In patients aged 16-25, who come under adult services, cautious treatment is required to prevent cerebral oedema.

There are a several clinical guidelines, governing treatment of DKA in adult patients such as those from the American Diabetes association, the Canadian Diabetes Association and the Joint British Diabetes Society (JBDS). There are points of difference amongst these guidelines that may cause inconsistencies amongst clinicians. The UK guidelines, initially written over a decade ago, but revised most recently in June 2021 will guide the treatment recommendations in this piece, which is aimed at hospital pharmacists and those governing clinical guidelines in Irish hospitals.

1. REFLECT - Before reading this module, consider the following: Will this clinical area be relevant to my practice?

2. IDENTIFY - If the answer is no, I may still be interested in the area but the article may not contribute towards my continuing professional development (CPD). If the answer is yes, I should identify any knowledge gaps in the clinical area.

3. PLAN - If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?

4. EVALUATE - Did this article meet my learning needs - and how has my practise changed as a result?Have I identified further learning needs?

5. WHAT NEXT - At this time you may like to record your learning for future use or assessment. Follow the 4 previous steps, log and record your findings.

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Diabetic Ketoacidosis in Adult Patients

Introduction:

Diabetic ketoacidosis (DKA) is a serious, life threatening emergency in patients with diabetes mellitus. DKA continues to be a common cause of hospital admission in type 1 diabetes mellitus (T1DM) and is the leading cause of mortality in young people with T1DM.[1]

DKA may be the first manifestation of T1DM in 25% of cases.[2] DKA may also occur in patients with type 2 diabetes (T2DM), known as ketosis-prone T2DM, which is more common in those of Afro-carribean, Asian or Hispanic backgrounds.[3]

Euglycaemic DKA (euDKA)- characterised by ketonaemia and acidosis- can occur in patients taking SGLT2 (Sodium-Glucose co-transporter 2 inhibitors)- dapagiflozin, canagiflozin, empagiflozin. ertugliflozin and sotagliflozin. euDKA may also occur in pregnant patients; patients with prolonged starvation; patients who were partially treated with insulin prior to admission; or due to acute alcohol intake.[3]

Pathogenesis, clinical features and diagnosis

DKA is caused by absolute or relative insulin deficiency, often coupled with increased concentration of counter-regulatory hormones, such as cortisol, glucagon, catecholamines and growth hormone.[2] This combination leads to hyperglycaemia, through failure of insulin-mediated cellular uptake of glucose. With the impairment of glucose uptake, an alternate energy source is provided by an increase in the formation of free fatty acids- acetoacetic acid and □ hydroxybutyrate, which lower pH and cause metabolic acidosis. The free fatty acids are oxidised to ketones (ketogenesis)- acetoacetic acid to acetone, which gives the characteristic fruity smelling breath associated with DKA. Glycogenolysis and gluconeogenesis in the liver further increase hyperglycaemia (see figure 1).

Euglycaemic DKA, caused by SGLT2 inhibitors, is thought to occur as a result of their mechanism of action, reducing serum glucose primarily by increasing glucosuria in the kidney. They also appear to directly stimulate release of glucagon from the pancreas. The glucosuria leads to decreased sodium reabsorption in the kidney, which in turn, increases ketone body reabsorption. Lower plasma glucose suppresses insulin release and further increases glucagon release from the pancreas. Increased glucagon-to insulin ratio results in increased lipolysis, fatty acid oxidation and ketone production by the liver.[4] A picture of ketosis and acidosis arises, without the usual hyperglycaemia characteristic of DKA. This can lead to delays in diagnosing euDKA. As such, patients presenting to hospital unwell, who are taking an SGLT2 inhibitor, should have their ketones checked, and if raised, their pH checked also.[2] The SGLT2 inhibitor should be stopped immediately and a HPRA Human Medicines Adverse Reaction Report completed. Whether the drugs can be restarted should be discussed with the diabetes team.[5]

DKA onset can be rapid- often within 24 hours and patients deteriorate quickly without treatment- coma or death can occur in 3-4 days.[3] Precipitating factors include: infection; myocardial infarction; surgery; omission of insulin; new onset of diabetes; and certain drugs, such as corticosteroids, thiazides and second generation antipsychotics.[2] In the case of T1DM, mistakenly omitting insulin in the context of illness with reduced oral intake is a common precipitant of DKA. Diabetes Ireland state that every patient and/or their carers should be given a verbal and written

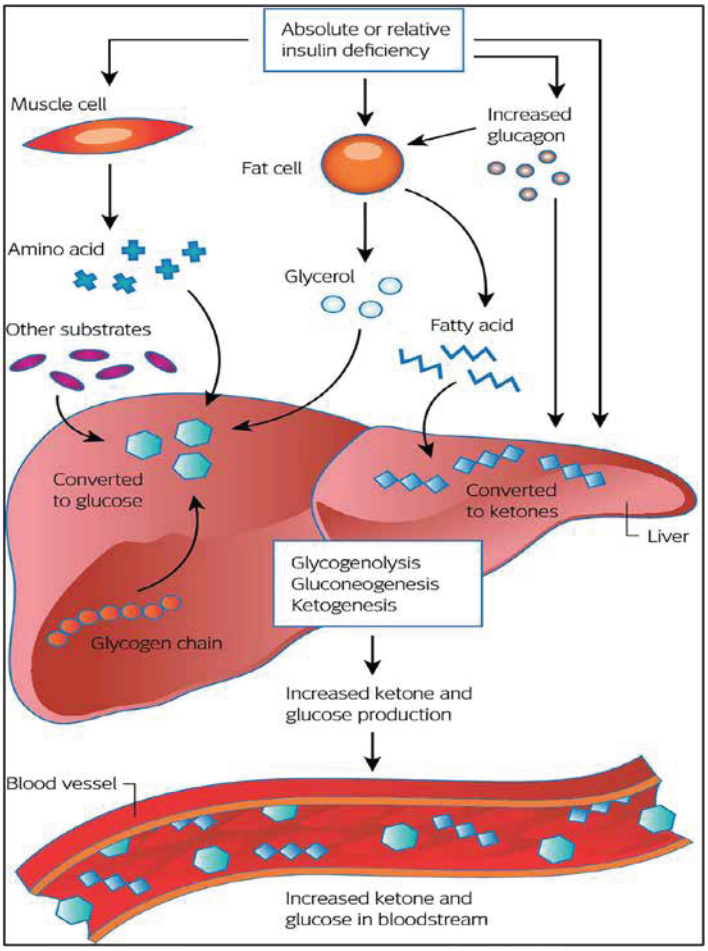

Figure 1: Pathogenesis of DKA. Reproduced with Permission. Misra S and Oliver N. Diabetic ketoacidosis in adults. (2015) BMJ; 351.

copy of individualised "sick day rules", which reiterates how to prevent loss of control of their diabetes during periods of illness.[6] Most importantly, for T1DM, this includes never stopping insulin, avoidance of dehydration, and increasing frequency of monitoring of blood glucose and ketones when unwell. Psychological issues associated with eating disorders and purposeful insulin omission, particularly in adolescent patients with T1DM, are well documented, occurring in up to 20% of recurrent DKA episodes in younger patients.[3] Factors leading to insulin omission in this population include fear of weight gain, fear of hypoglycaemia, rebellion from authority and the stress of chronic disease.[7] Cocaine use has also been associated with recurrent DKA.[2,7]

Patients with DKA can present with polyuria, polydipsia and weight loss. They may also have clinical features of underlying infection, abdominal pain, nausea, vomiting, and drowsiness. Metabolic acidosis may induce compensatory hyperventilation (called Kussmaul respirations).[5,7] According to the JBDS guidelines[5,8] DKA is diagnosed based on a triad of criteria:

1) Diabetes- hyperglycaemia (blood glucose > 11.0 mmol/L) or a previous diagnosis of diabetes mellitus;

2) Ketonaemia or significant ketonuria- plasma ketones >3.0 mmol/L or a reading of +2 or more on standard urine sticks;

and 3) Acidosis: a venous pH of <7.3 and/or a bicarbonate of <15 mmol/L.

For a diagnosis of DKA all three criteria must be present. In euglycaemic DKA, blood glucose may be in normal range or only mildly raised.[2]

Severe DKA

Management in a high dependency setting should be considered for patients with severe DKA (presence of any of the symptoms listed in table 1 below), pregnant patients, young patients (18-25 years) and patients with heart failure, renal failure or any other serious comorbidities.[5]

Severe DKA is the most common cause of diabetes-related death in children and adolescents. Most DKA-related deaths occur due to cerebral oedema, which bears greater risk in paediatric patients and those aged 25 and under.[5] For this reason, treatment of paediatric DKA differs from adult management. In Ireland, there is a National Clinical Practice Guideline for the management of paediatric DKA.[9] The British Society for Paediatric Endocrinology and Diabetes (BPSED) have also published a recent clinical guideline (2020).[10] Young patients who come under adult services (aged 16-25) may be treated using adult guidelines but should be closely monitored for signs of clinical oedema, such as headaches, altered consciousness (as measured by Glasgow Coma Score) and agitation/aggression.[5]

Management:

Management of DKA has three important remits: 1) fluid replacement to address dehydration, hypovolaemia and potential shock; 2) replacement of insulin to reduce ketosis and treat hyperglycaemia; and 3) maintain potassium homeostasis.

Fluid Replacement:

In adult patients, the severity of dehydration can be assessed using pulse and blood pressure, taking age, gender and concomitant medication into account. Systolic blood pressures (SBP) below 90 mmHg on admission are likely to be caused by low circulating volume, but could be down to factors such as heart failure or sepsis.[5] JBDS guidelines recommend initial fluid resuscitation to shocked patients (SBP 90 mmHg) with 500mL bolus of 0.9% sodium chloride given over 10-15 minutes. If SBP remains below 90 mmHg, this should be repeated.

Once SBP is above 90 mmHg, the fluids regimen outlined in table 2 below is recommended for an average adult, weighing 70kg. Caution is recommended in elderly, renal impairment, heart failure (CCF) and young or pregnant patients, where cerebral or pulmonary oedema could be a risk. Beyond the timescale outlined, further fluid therapy should be guided by fluid status.[5] Once blood glucose has dropped to below 14 mmol/L, 10% glucose should be run alongside 0.9% sodium chloride.[5]

Electrolyte abnormalities are common in DKA, but potassium replacement, titrated to potassium levels as per table 2, is the most important. Patients may present with normal or elevated potassium on admission (due to insulin deficiency and hyperosmolality,

Table 1. Symptoms of Severe DKA

Severe DKA (indicated by the presence of any of the following):
• *Ketones greater than 6 mmol/L*
• *Bicarbonate (HCO_3^-) below 5 mmol/L*
• *Venous pH below 7.1*
• *Hypokalaemia on admission (potassium less than 3.5 mmol/L)*
• *Glasgow Coma Score (GCS) below 12*
• *Systolic BP less than 90 mmHg*
• *Oxygen saturation below 92% (assuming normal baseline respiratory function)*
• *Heart rate above 100 or below 60 bpm*
• *Anion gap above 16 mmol/L {Anion gap = $(Na^+ + K^+) – (Cl^- + HCO_3^-)$}*

Table 2: Fluid replacement regime for Adult DKA patients

Fluid	Rate
0.9% Sodium Chloride 1L	*Over 1 hour {given in first hour or when SBP>90 mmHg following fluid bolus(es)}*
0.9% Sodium Chloride 1L +/- Potassium Chloride*	*Over 2 hours*
0.9% Sodium Chloride 1L +/- Potassium Chloride*	*Over 2 hours*
0.9% Sodium Chloride 1L +/- Potassium Chloride*	*Over 4 hours*
0.9% Sodium Chloride 1L +/- Potassium Chloride*	*Over 4 hours*
0.9% Sodium Chloride 1L +/- Potassium Chloride*	*Over 6 hours*

Caution in elderly, CCF, renal failure, adolescence, pregnancy (risk of cerebral and pulmonary oedema)

- *K^+ >5.5- nil, recheck potassium levels in 2 hours*
- *K^+ 3.5-5.5 - 40mmol/L potassium chloride*
- *K^+ <3.5- Urgent senior medical review. Higher concentrations of potassium may be required*
- *Caution if patient anuric*

which drive potassium out of cells), but total body potassium is low due to osmotic diuresis and secondary hypoaldosteronism.[3] Extracellular potassium levels can fall rapidly with insulin infusion, which stimulates cellular uptake of potassium; fluids, which have a dilutional effect; and correction of acidosis. Patient's urine output should be monitored and potassium replacement should be cautious if the patient is oliguric.[5]

In-keeping with international safety warnings and the Irish Medicines Safety Network (ISMN) Best Practice Guidelines for the Safe Use of Intravenous Potassium in Irish Hospitals (2020), premixed bags of 0.9% sodium chloride with potassium chloride at concentrations of up to 40 mmol/L should be used where possible, with higher potassium concentrations only considered in critical care settings.[11]

The use of intravenous bicarbonate is not recommended routinely in DKA as it can paradoxically worsen acidosis and increase the risk of hypokalaemia and cerebral oedema. In addition to potential harmful effects, there is little evidence of benefit. Bicarbonate infusions should only be considered by senior level clinicians, if pH <7 and ideally, in a critical care setting.[2,3,5]

Fluid replacement in paediatric patients:

Whilst this CPD deals with DKA in adults, it is worth mentioning that management of DKA differs in paediatric patients, where volume restoration is gradual to avoid cerebral oedema. The current HSE National Clinical Guideline[9] recommends 10 mL/kg of 0.9% NaCl over 30 minutes, repeated if necessary to treat shock. BPSED[10] recommend that patients who are not shocked receive 10 mL/kg of 0.9% NaCl over 60 minutes, while shocked patients are given 20 mL/ kg 0.9% NaCl over 15 minutes, followed by up to two boluses of 10 mL/kg. Thereafter BPSED recommend inotropes should be considered.

Subsequent fluids are carefully calculated based on weight and % dehydration and given slowly over 48 hours with careful monitoring to avoid cerebral oedema. For patients aged 16-18 treated under adult services, the adult treatment guidelines should be used to avoid mistakes due to staff unfamiliarity with the paediatric treatment regimens. Those admitted to a paediatric ward should be treated using paediatric clinical guidance. As stated above, patients aged 16-25 under adult services should be closely monitored for cerebral oedema.

Insulin Therapy:

Once fluids have been initiated, insulin replacement can commence, ideally via a second peripheral access line.[5] The American Diabetes Association (ADA)[12] and JBDS now both recommend a fixed rate intravenous insulin infusion (FRIII), rather than a variable rate insulin infusion (VRIII, previously known by the ambiguous term "sliding scale"). It is now recognised that blood glucose levels are a poor marker for serum ketosis and altering insulin rate based on glucose levels may lead to inadequate resolution of ketoacidosis. The disadvantage with using FRIII is that blood glucose must be measured hourly to avoid hypoglycaemia and 10% glucose infusion must be started once serum blood glucose <14 mmol/L. The FRIII is continued until resolution of ketosis, defined by pH>7.3 and capillary ketones<0.6mmol/L. In addition to starting glucose 10% alongside the insulin infusion, the 2021 JBDS guidelines also recommend considering de-escalation of the insulin dose from 0.1 to 0.05 units/kg/hour once blood glucose <14 mmol/L. This recommendation is due to significant rates of hypoglycaemia (27.6%) and hypokalaemia (67%) reported on the national audit of a previous version of the guideline.[5]

FRIII is given via an infusion pump. It is made up of 50 units of

Table 3: Fixed rate intravenous insulin infusion. (JBDS, 2021)[5]

Patient weight (kg)	Insulin dose (units/hour) when blood glucose >14 mmol/L (0.1 units/kg/hour)	De-escalated insulin dose (units/hour) when blood glucose <14 mmol/L (0.05 units/kg/hour)
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
120-129	12	6
130-139	13	6.5
140-150	14	7
>150	15 (initial doses >15 units should only be under specialist supervision)	7.5

Summary of Recommendations for treating DKA in adult patients

Intravenous fluids	Shock (SBP < 90 mmHg)- give 500mL 0.9% NaCl over 15-20 minutes SBP still <90 mmHg, repeat if necessary
	Not shocked

0.9% NaCl 1L	Over 1 hour
0.9% NaCl 1L (+/- KCl 40 mmol)	Over 2 hours
0.9% NaCl 1L (+/- KCl 40 mmol)	Over 2 hours
0.9% NaCl 1L (+/- KCl 40 mmol)	Over 4 hours
0.9% NaCl 1L (+/- KCl 40 mmol)	Over 4 hours
0.9% NaCl 1L (+/- KCl 40 mmol)	Over 6 hours

	Additional fluids to be based on clinical assessment
	Potassium replacement if [K^+] 3.5-5.5 mmol/L (aim [K^+] 4-5.5 mmol/L) If < 3.5 mmol/L higher concentrations of potassium may be required (consider critical care). > 5.5 mmol/L omit and monitor hourly.
	Start glucose 10% 500mL over 4 hours when blood glucose <14 mmol/L (run concurrently with 0.9% NaCl)
Insulin	Dilute 50 units human soluble insulin (Actrapid® or Humulin S ®) in 50mL NaCl 0.9% Start a FRIII at a rate of 0.1 units/kg. Continue long-acting/human insulin analogues
	Aims: Reduction of ketones by 0.5 mmol/hour, reduction of blood glucose by 3 mmol/hour and increase in bicarbonate by 3 mmol/hour If ketones and blood glucose not dropping sufficiently, check insulin infusion pump, cannula and lines, before increasing by 1 unit/hour Continue FRIII until ketones < 0.6mmol/L and pH >7.3
	Once blood glucose <14 mmol/L, consider reducing insulin dose to 0.05 units/kg/hour
	If patient eating and drinking, start subcutaneous insulin If not eating and drinking, switch to VRIII When switching from IV insulin (FRIII or VRIII) to subcutaneous, give subcutaneous dose 30-60 minutes prior to stopping infusion and with a meal.

human soluble insulin (Actrapid® or Humulin S®) made up to 50mL with 0.9% sodium chloride. JBDS, unlike ADA, do not recommend an initial priming dose of insulin. See table 3 for JBDS recommended FRIII dosing. They state doses in excess of 15 units per hour should be discussed with the diabetes inpatient team.

JBDS recommend hourly monitoring of blood glucose and ketones. Venous pH, bicarbonate and serum potassium should be checked at 60 minutes, 2 hours and 2 hourly thereafter or until transition to subcutaneous insulin.[5]

The treatment targets with FRIII are to reduce blood ketones by 0.5 mmol/L/hour; reduce blood glucose by 3.0 mmol/L/hour (whilst avoiding hypoglycaemia), increase bicarbonate by 3.0 mmol/L/hour and maintain potassium between 4.0 and 5.5 mmol/L. If these targets are not being achieved, the the pump, connections and line patency should be checked before consideration given to increasing the infusion rate by 1 unit/hour increments until the required response is attained.

Continuation of basal insulin

JBDS guidelines recommend basal insulin is continued in patients who were taking prior to admission, at their pre-admission dose and time. They state that continuation of long acting basal subcutaneous insulin analogues (Levemir®, Lantus®, Toujeo® and Tresiba®) provides background insulin when the IV insulin is discontinued, avoiding rebound hyperglycaemia. Short acting insulin, mixed analogues and oral hypoglycaemic agents should be held with IV insulin infusion. JBDS recommendations[5,8] also state that human analogues (Insulatard®, Humulin I®, Insuman Basal) may also be continued on the basis that there is not much difference between the onset of action and duration of actions of human basal insulin compared with the long acting analogues, however this has not yet been investigated in quality trials, so is at the discretion of the unit treating the patient.

In patients who were not taking basal insulin prior to DKA admission (e.g. those newly diagnosed with T1DM), the initiation of a long acting analogue is recommended at a dose of 0.25 units/kg given once a day. This is based on one small randomised controlled trial which showed that initiating a long acting analogue (e.g. Lantus® or Levemir®) alongside FRIII may reduce the incidence of rebound hyperglycemia when the insulin infusion is discontinued, without increasing the risk of hypoglycemia.[13]

Resolution of symptoms:

Once DKA is resolved (pH >7.3 and ketones 0.6 mmol/L) and patient is eating and drinking, they can be switched back to their usual subcutaneous insulin regime. Urine ketones can persist and should not delay transfer to subcutaneous insulin in the context of overall clinical recovery. If their HbA1C suggests a poor level of control, their insulin regime should be reviewed by a specialist diabetes team.[5]

If patients are not eating and drinking, they can be switched to a variable rate intravenous insulin infusion (VRIII, previously known as a sliding scale). When switching to subcutaneous insulin, the short acting analogue should be given 30-60 minutes prior to stopping intravenous insulin infusion (FRIII or VRIII), and alongside a meal.[5,8]

Insulin naïve patients should ideally be seen by a specialist diabetes team, who would advise on a suitable insulin regime as there are a number of factors which may affect their insulin sensitivity, such as age, weight and degree of glycaemic control. An initial total daily dose of insulin of approximately 0.5-0.75 units/kg may be used. For a basal-bolus regime, 50% should be given as long-acting basal insulin with the evening meal and the remainder as a short-acting analogue, divided equally across the morning, lunchtime and evening meals.[14] Close monitoring of blood sugar and ketones is required.

References on request