Diabetic Ketoacidosis in Adults: Part 3. Special situations

Ali Azkoul[1], Sing Sim[1] and Victor Lawrence[2]

1. Specialist Registrar in Diabetes and Endocrinology, St Mary's Hospital, Newport, Isle of Wight, UK
2. Consultant in Diabetes and Endocrinology, Honorary Senior Lecturer University of Portsmouth, St Mary's Hospital, Newport, Isle of Wight, UK

Correspondence:
Victor Lawrence
victor.lawrence@nhs.net

Submitted: December 2021
Accepted: March 2022
Published: May 2022

Citation: Azkoul et al. Diabetic Ketoacidosis in Adults: Part 3. Special situations, South Sudan Medical Journal 2022;15(2):71-75 DOI: https://dx.doi.org/10.4314/ssmj.v15i2.8

ABSTRACT

Prompt diagnosis and treatment of Diabetic Ketoacidosis (DKA) with the correct administration of intravenous (i.v.) fluids, fixed rate insulin infusion (FRII) and guideline-based K^+ replacement are essential for optimum outcomes. However, treatment guidelines may need to be adapted in special situations such as pregnancy, end stage renal disease or where resources, such as infusion pump equipment, may not be available. Children require treatment according to specific paediatric guidelines particularly to minimise the risk of cerebral oedema. Although DKA is a serious and complex medical emergency, skilled medical care can reduce mortality rates to below 1%.

Key words: Diabetic ketoacidosis, pitfalls, pregnancy, renal disease, infection, acute abdomen.

INTRODUCTION

In this, the third of a three-part review of Diabetic Ketoacidosis (DKA) in adults, we focus on pitfalls in the management of DKA and on special situations where the usual management outlined in Part 2[1] may need to be adapted. Pitfalls refer to situations where clinicians managing DKA may be misled into taking incorrect decisions unless they are familiar with the issues. They also include some areas of controversy such as in the indications for the use of sodium bicarbonate infusions in patients with very severe acidosis.

PITFALLS IN THE MANAGEMENT OF DKA

Hyponatraemia

It is common for DKA patients to be initially hyponatraemic. This is due to hypertonicity driving water from the intracellular to extracellular fluid compartments which dilutes the extracellular concentration of sodium ($[Na^+]$). With improvement of hyperglycaemia, $[Na^+]$ will rise. The following formula may be used to 'correct' the $[Na^+]$ concentration for hyperglycaemia.[2]

Corrected Na^+ = Measured Na^+ + 2.4 {(glucose (mmol/L) -5.5)/5.5}

In effect, this predicts the level to which the measured $[Na^+]$ will rise after correction of hyperglycaemia. If this prediction suggests that the $[Na^+]$ may rise to a very high level (say >155-160 mmol/l), then cautious use of half-normal (0.45%) saline rather than 0.9% Saline may be considered during the period of volume restoration. It is worth pointing out that although there is considerable controversy over the use of half-normal (0.45%) saline solutions in the management of DKA, a patient whose blood glucose level has fallen to below 14 mmol/l who is treated according to the protocol recommended in the second part of this series may be receiving simultaneous infusions of both normal saline and 10% glucose which, once the glucose has been disposed of by metabolism, storage or excretion, may in effect amount to an infusion of hypotonic saline.

High Total White Cell Count

A raised total white blood cell count may be observed in DKA even in the absence of infection. This is thought to be a consequence of catecholamine secretion in response to hypovolaemia.

Infection

Infection is a common cause for DKA. It needs to be considered and treated if present but not all patients presenting with DKA have an infection requiring treatment. DKA can sometimes be misdiagnosed as infection (particularly malaria or an 'acute abdomen'). Occasionally a severe infection such as meningitis may precipitate, but then be masked by, DKA as both conditions may cause drowsiness, low blood pressure, acidosis and renal failure. Until recently, there has been no absolute failsafe method for detecting the presence of a serious infection requiring treatment during DKA other than by taking a careful history and appropriate samples e.g. blood or urine cultures, being aware of the risk of masked infection and having a low threshold for reassessment particularly where progress in resolution of DKA and/or clinical improvement is not as expected. However, there is some evidence that procalcitonin measurement, where available, particularly in association with documentation of fever >38^{0}C may be helpful in both ruling in, and in excluding, serious bacterial infection in patients with DKA.[3]

Raised amylase

Raised serum amylase is common in DKA, even in the absence of pancreatitis. Abdominal pain is also common due to an acute ketone-induced gastroparesis. However, DKA may also be precipitated by and mask an acute abdomen so careful clinical observation is required particularly where recovery is not progressing as rapidly as expected.

Ketones

Measurement of 3-β-OHB through capillary blood samples provides the best indicator of ketone body levels. Urinary ketone tests rely on nitroprusside reactions which have a high affinity towards acetoacetate and acetone but not 3-β-OHB. This can provide false reassurance in the initial stages of DKA. During DKA, low insulin levels and high counter-regulatory hormones increase 3-β-OHB: acetoacetate ratio to 10:1. With successful treatment, 3-β-OHB levels decrease whilst acetoacetate levels increase. Measuring urinary acetoacetate levels as the patient improves may therefore over-estimate the degree of ketosis which sometimes unnecessarily prolongs treatment intensity.[4]

Bicarbonate use

The acidaemia in patients with DKA is caused mainly by ketoacids but there may be additional contributions from renal impairment and lactic acidosis. The use of bicarbonate is generally unnecessary and potentially harmful as it could reduce serum [K^+], interfere with tissue oxygen delivery through effects on the oxy-haemoglobin dissociation curve, prevent hyperventilation and it may cause a paradoxical worsening of central nervous system acidosis because CO_2 diffuses through the blood brain barrier faster than the infused bicarbonate. At a pH of 6.9-7.1, administering bicarbonate does not improve recovery outcomes and could cause harm. At a pH of <6.9, these are no good data but many would fear the imminent development of cardiovascular collapse and would give a sodium bicarbonate infusion to correct the pH to >7.0. [5,6]

Hyperchloraemic metabolic acidosis

During treatment of DKA, large volumes of administered Normal Saline frequently result in a hyperchloremic metabolic acidosis as the kidneys preferentially excrete ketones over chloride anions. Up to 90% of patients remain hyperchloremic between 8 to 20 hours.[7] In general, this form of acidosis is rarely a major clinical issue and will resolve spontaneously within hours to a day or two. It does not require specific treatment (beyond stopping any unnecessary Normal Saline infusions after resolution of ketoacidosis and restoration of oral fluid intake) and does not indicate delayed resolution of DKA. The mistake often made is to assume that the DKA is not resolving even though ketones (and lactate) are low because of the persisting low bicarbonate concentration and this is a particular risk where ketone measurement is not available and treatment is being monitored with HCO_3^- measurement.

Cerebral Oedema

The development of cerebral oedema is very rare in adults treated according to these guidelines. If there is deterioration of consciousness despite improved metabolic state, especially accompanied by signs of raised intracranial pressure such as bradycardia and hypertension, consider brain imaging (ideally by MRI if available, otherwise CT) to look for cerebral oedema or another CNS insult that could depress conscious level (e.g., stroke, venous sinus thrombosis, cerebral haemorrhage). Management of cerebral oedema will require specialist support and generally includes mannitol, hypertonic saline and dexamethasone. Although rare in adults, cerebral oedema is a real risk in children who should be treated according to specific paediatric guidelines (see the section on 'Children and young people' below which includes an approach to treatment of suspected or proven cerebral oedema).

Glucometer reading 'Hi'

Bedside glucometers using test strips will usually register a result of 'Hi' when sampled capillary blood glucose levels exceed a maximum limit for the test, typically around 28-33 mmol/l depending on brand. It is important that a laboratory (or blood gas analyser) blood glucose level is then obtained so that the actual fall in blood glucose levels may be appreciated, and insulin infusion rate adjusted if appropriate.

Distinguishing Hyperosmolar Hyperglycaemic State (HHS) from DKA

Distinguishing these two diabetes emergencies is usually straightforward on the basis of the presence or absence of ketoacidosis (favouring DKA) and hyperosmolality (usually >320 mOsm/Kg) without significant acidosis favouring HHS. HHS is typically encountered in older individuals with type 2 diabetes whose blood glucose levels are typically ≥30 mmol/L and who have profound hypovolaemia. However, the distinction may be less clear cut particularly as there is no universally accepted biochemical criteria for the diagnosis of HHS which remains a clinical diagnosis supported by characteristic laboratory findings. Acidosis (pH<7.3, HCO_3^-<15 mmol/l) may accompany HHS but when it does so, is typically due to the accumulation of lactate ions (lactic acidosis) and/or due to associated Acute Kidney Injury rather than primarily due to the accumulation of ketones. In this situation, blood hydroxybutyrate concentrations will be well below the level used as a diagnostic criterion for DKA (i.e., below 3.0 mmol/l) and the treatment approach should be directed towards management of HHS rather than DKA. In some cases of HHS with marked hyperosmolality (>320 mOsm/Kg) and profound dehydration, there will be significant acidosis (pH<7.3, HCO_3^- <15 mmol/l) associated with ketone accumulation to levels more typically associated with DKA (i.e., blood hydroxybutyrate > 3.0 mmol/l or ketonuria ≥2+). In this situation, the diagnosis is best considered to be a mixed form of HHS/DKA and treatment would be as for DKA with possible adaptation for the age, co-morbidity, precipitant, degree of hypovolaemia and degree of hyperosmolality present. Expert involvement may be helpful in such mixed cases although the DKA pathway, particularly as regards insulin infusion, should be followed initially.

DKA IN SPECIAL SITUATIONS

Lack of availability of an insulin infusion pump

In circumstances of limited resources, it may not be possible to use fixed rate insulin infusions with shortage of infusion pumps or trained nursing staff. In this situation, a loading dose of soluble insulin intramuscularly (10-20 units) followed by 5 units hourly can be given.[2]

Alternatively, if available, rapid acting insulin analogues may be administered subcutaneously on an hourly basis in the management of mild and moderate DKA. This has shown similar outcomes to FRII when combined with fluid rehydration.[8] A suitable regime is to give an initial s.c. insulin injection of 0.3 units/kg body weight, followed by 0.1 units/ kg/ hour s.c. until blood glucose reaches 13.8 mmol/l at which time the insulin is reduced to 0.05 units/ kg/ hour, and the IV fluids changed to Dextrose (D) 5% in 0.45% saline to maintain blood glucose at about 11.1 mmol/l until resolution of DKA. Alternatively, patients can be managed with 2-hourly s.c. injections so that they receive an initial dose of 0.3 units/ kg followed by 0.2 units/kg 1 h later and then again every 2 hours until blood glucose reaches 13.8 mmol/l. At that time, the insulin dose is reduced to 0.1 units/kg every 2 hours, and the IV fluids changed to D5% in 0.45 saline to keep blood glucose at about 11.1 mmol/l until resolution of DKA.[8]

DKA in end stage renal disease or dialysis

This is an uncommon situation since insulin clearance by the kidneys is reduced in end stage renal disease (ESRD) and failure to generate an osmotic diuresis in response to hyperglycaemia further reduces the risk of DKA. In fact, hyperglycaemia may paradoxically lead to fluid volume expansion through increased thirst and hence fluid intake with absence of the osmotic diuresis that leads to dehydration in non-renal patients.[9] Fluids should be administered with great caution in apparently hypovolemic patients with 250ml boluses (0.9% NaCl or Dextrose 10% as appropriate) in this situation.

The insulin infusion rate in ESRD is generally similar to that in patients with normal renal function but more caution is needed as the risk of hypoglycaemia is greater due to reduced insulin clearance. Once blood glucose is < 14 mmol/l, strongly consider reducing the rate of insulin infusion to 0.05 units/kg/hour. More concentrated dextrose solutions may be needed to avoid overload.[9] Potassium excretion is impaired in renal failure and together with the lack of osmotic diuresis; there is little or no potassium loss through the kidneys. On the contrary, end stage renal failure patients with severe acidosis may develop hyperkalaemia and may require dialysis. Potassium should be added to infusion fluids with great caution, if at all, in patients with ESRD.

Euglycaemic DKA with SGLT2 inhibitors

Euglycaemic DKA is a rare complication of Sodium-glucose Cotransporter-2 (SGLT2) inhibitors (e.g., empagliflozin, canagliflozin, dapagliflozin). Patients may develop DKA despite having a blood glucose level

of <11mmol/L. SGLT-2 inhibitors are linked to a small increased risk of diabetic ketoacidosis in individuals with both type 1 and type 2 diabetes. It is important to note that urine testing may be unreliable in detecting the development of ketoacidosis in this situation as SGLT2 inhibitors may impair urinary ketone excretion so blood ketone testing should be used in patients taking these drugs in whom DKA is suspected. As always, prevention is key and patients at risk of ketoacidosis (e.g., those with type 1 diabetes, ketosis prone type 2 diabetes or very poorly controlled type 2 diabetes who would best initially be treated with insulin) should not generally be prescribed SGLT2 inhibitors. Even in those not considered to be at high risk, ketoacidosis secondary to SGLT2 inhibition can develop in dehydration, stress, starvation, excessive alcohol consumption, acute medical illness or other catabolic states which shift metabolism to fat dependence and these agents should be stopped during such intercurrent illness.[10]

If DKA is confirmed in this situation, the SGLT-2 inhibitor should be stopped immediately and ketoacidosis treated conventionally (noting that glucose infusion may be required from the outset). Use of a variable rate insulin infusion (VRII) rather than a fixed rate insulin infusion may be needed to avoid hypoglycaemia and hypokalaemia.[10]

Pregnancy

DKA in pregnancy may occur in women with type 1 diabetes, type 2 diabetes or gestational diabetes and presents particular risks to the woman and her unborn child and specific challenges in its management.

Prevention is vital and most importantly includes the provision of specialist services to diagnose and treat dysglycaemia during pregnancy in women with both pre-existing and gestational diabetes mellitus. Care should be taken to titrate insulin in pregnant women receiving corticosteroids to promote foetal lung maturation in situations of anticipated pre-term labour (doses typically need to rise by 25-40% or more) and to avoid the use of sympathomimetic tocolytic agents (e.g., ritodrine, terbutaline) where possible (or for carefully titrated insulin infusion where this cannot be avoided).

In normal pregnancy, there is a state of respiratory alkalosis with a compensatory reduction in bicarbonate concentration which reduces the buffering capacity of the blood thereby reducing the threshold for the development of metabolic acidosis. There is an accompanying insulin resistance in pregnancy that may further predispose to DKA development. Aside from the precipitants of DKA for adults in general, specific factors during pregnancy include protracted vomiting (hyperemesis gravidarum) and the administration of specific drugs with counter-regulatory hormone type effects such as steroids for fetal lung maturation or tocolytic sympathomimetic agents. In women at risk of DKA, these should be avoided where suitable alternatives can be used instead. Euglycaemic DKA (DKA with presenting blood glucose levels <11 mmol/l) is more common in pregnancy, due to the glucose disposal of the feto-placental unit, increased renal glucose losses during pregnancy, increased maternal glucose utilization and increased volume of distribution of glucose. These effects will be augmented where DKA is precipitated by excessive vomiting or starvation which will dehydrate and deplete hepatic glycogen stores respectively. Euglycaemic DKA requires infusion of glucose from the outset in order to permit insulin infusion (either as fixed or variable rate) in sufficient dose to suppress ketogenesis. Consideration should be given to administering thiamine iv prior to glucose particularly where starvation/hyperemesis has been longstanding to prevent the development of Wernicke's encephalopathy.

DKA in pregnancy may cause maternal complications such as acute kidney injury, adult respiratory distress syndrome, cerebral oedema or death. Fetal mortality has been estimated as being up to 36% but permanent fetal morbidity may also occur due to hypoxia, reduction in cerebral glucose uptake or utilization, exposure to a period of reduced uteroplacental function, electrolyte disturbances and maternal or fetal cardiac dysrhythmia.

A decision to deliver should be individualized and multidisciplinary but in general, the focus will be on restoration of maternal cardiovascular and metabolic stability rather than delivery unless consideration of maternal wellbeing, gestational age and fetal condition (e.g., fetal heart monitoring) suggest a potential benefit from delivery.[11]

Children and young people under 18 years of age

The management of children with DKA differs in a number of important ways from that of adults and is not covered here in detail. Children are more vulnerable to the development of cerebral oedema during DKA treatment in particular and management is designed to minimize the risk of this whilst ensuring prompt resolution of DKA. The reader is referred to comprehensive guidelines on the management of DKA in children for further information.[12]

SUMMARY AND CONCLUSIONS

Prompt diagnosis and treatment of DKA with the correct rates and volumes of i.v. fluids together with fixed rate insulin infusion and guideline-based K+ replacement form the mainstay of treatment.

Treatment protocols may need to be adapted in special situations such as pregnancy, end stage renal disease or where resources such as infusion pump equipment may not be readily available and children require treatment

according to dedicated paediatric guidelines particularly to minimise the risk of cerebral oedema.

Although DKA is a serious and complex medical emergency, skilled medical care can reduce mortality rates to below 1%.

The other papers in this series are on Pathogenesis and Diagnosis[13] and Management.[1]

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