Diagnosis and treatment of diabetic ketoacidosis

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Abstract
Diabetic ketoacidosis (DKA) is the most frequent hyperglycaemic acute diabetic complication. Furthermore it carries a significant risk of death, which can be prevented by early and effective management. All physicians, irrespective of the discipline they are working in and whether in primary, secondary or tertiary care institutions, should be able to recognise DKA early and initiate management immediately.

Introduction
Diabetic ketoacidosis (DKA) is a common complication of diabetes with an annual occurrence rate of 46 to 50 per 10 000 diabetic patients. The severity of this acute diabetic complication can be appreciated from the high death-to-case ratio of 5 to 10%. In Africa the mortality of DKA is unacceptably high with a reported death rate of 26 to 29% in studies from Kenya, Tanzania and Ghana. It is a complication of both type 1 and type 2 diabetes mellitus, although more commonly seen in type 1 diabetic patients. Of known diabetic patients presenting with DKA about one-quarter will be patients with type 2 diabetes. In patients presenting with a DKA as first manifestation of diabetes about 15% will be type 2. This correlates well with data from South Africa suggesting that one-quarter of patients with DKA will be type 2 with adequate C-peptide levels and the absence of anti-GAD antibodies.

This review will focus on the principles of diagnosis, monitoring and treatment of DKA, with special mention of new developments and controversial issues.

Clinical features
DKA evolves over hours to days in both type 1 and type 2 diabetic patients, but the symptoms of poor control of blood glucose are usually present for several days before the onset or presentation of ketoacidosis. The clinical features of DKA are non-specific and patients may present with complaints of nausea, vomiting and weakness, polyuria, polydipsia, abdominal pain and weight loss. In a study by Newton and Raskin the frequency of symptoms in patients were as follows: nausea 83.4%, vomiting 78.5%, polyuria 75.2%, polydipsia 74.4%, abdominal pain 51.2%, weight loss 42.1% and polyphagia 33.1%. Abdominal pain is a misleading manifestation, which can result in the late or misdiagnosis of DKA. Abdominal pain appears to be related to the presence of metabolic acidosis, but the exact mechanism is poorly understood. Often in children the abdominal pain may clinically mimic the findings of an acute abdomen.

Physical examination may also show evidence of dehydration: loss of skin turgor, dry mucus membranes, tachycardia and hypotension. In the study by Newton and Raskin, patients had an average heart rate of 117 beats per minute, but most patients had a slightly elevated systolic and diastolic blood pressure (mean 135 ± 23 and 85 ± 15). Most patients were normothermic or hypothermic despite the high frequency of infection present and it seems that severe hypothermia carries a poor prognosis. Patients with DKA can present with varying levels of consciousness with the majority of patients being alert and less than 20% present comatose. Abnormalities detected in mental status examination seem to correlate best with an increase in osmolality. Furthermore, patients with severe metabolic acidosis will usually have distinctively rapid and deep breathing (Kussmaul's breathing).

Diagnostic criteria
In 2003 the American Diabetes Association (ADA) modified the diagnostic criteria of DKA with the introduction of severity categories of mild, moderate and severe (see Table I).

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>&gt; 13.9</td>
<td>&gt; 13.9</td>
<td>&gt; 13.9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
<td>&lt; 7.00</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
<td>15–18</td>
<td>10–14.9</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Anion gap</td>
<td>&gt; 10</td>
<td>&gt; 12</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Sensorium</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>

Adapted from ADA position statement

The diagnosis of DKA consists of a triad of hyperglycaemia, ketonaemia and metabolic acidosis.

Most DKA guidelines indicate that hyperglycaemia of more than 13.9 mmol/l is necessary for the diagnosis of DKA, however this is not an absolute requirement, as DKA without hyperglycaemia has been reported. DKA without hyperglycaemia is mostly reported during pregnancy, and in patients with prolonged vomiting or starvation. It can also occur in patients with liver failure or in alcohol abusers.
Ketone bodies are produced in the liver from acetyl-CoA liberated during lipolysis from fatty acids. For DKA to develop, an absolute or relative insulin deficiency must be present. Three ketone bodies are produced: acetone (resulting in the fruity odour of DKA patients), acetoacetate and β-hydroxybutyrate (β-OHB); β-OHB is the most prominent contributor to metabolic acidosis in patients with DKA. Acetone does not contribute to acidosis and is not usually measured as such. Acetoacetate can be measured in the urine with a urine dipstick utilising the nitropruside reaction. As DKA resolves, β-OHB are oxidised to acetoacetate. Therefore, if only a urine ketone dipstick procedure is done it might give the impression that the condition is not improving. Currently blood ketones can be measured with a point of care (bedside) meter utilising capillary finger prick blood. This measures β-OHB directly and accurately. A capillary β-OHB value of 3 mmol/l and above has a positive likelihood ratio of 15 for the presence of DKA. It is recommended by the ADA that the blood ketone measurement of β-OHB is preferable to urine measurement for the diagnosis and monitoring of DKA.

Precipitating events that can trigger DKA
The most common precipitating event for the development of DKA is infection, which accounts for 28 to 45% of cases. Pneumonia or any lung disease that can influence oxygenation, and can lead to respiratory failure, should always be considered as extremely serious because it may impair respiratory compensation of metabolic acidosis. The second most common precipitating event worldwide is the omission of insulin. The third most common cause is the first manifestation of new onset diabetes. Other common precipitating events include cardiovascular events such as a stroke, myocardial infarction and peripheral vascular disease with gangrene. In a Kenyan study, 34% of DKA events were due to missed insulin injections, 23.4% to overt infection and only 6.4% had both infection and missed insulin injections. Infection sites included respiratory, genito-urinary and septicaemia. DKA is about 10 times more common in patients with schizophrenia. This may be due to the use of the newer antipsychotic agents dozapine and olanzapine.

The physician caring for diabetic patients should enquire and be aware of the high risk related to psychological and socioeconomic factors. A study of urban African Americans states that 50% of patients presenting with DKA as a result of non-compliance of insulin did so because of lack of money to buy insulin or to pay for transport to the hospital. Another 14% failed to comply with the prescribed insulin injections due to behavioural or psychological reasons. All diabetic patients should be educated and trained about what to do when they become ill, until they are able to see a health care professional.

Monitoring to recovery of DKA
Due to the seriousness and high risk of relapse or deterioration in patients with DKA, it is important to monitor progress frequently. Monitoring should include clinical parameters such as blood pressure, pulse rate, hydration status and mental status. Laboratory and bedside biochemical measurements should be assessed regularly. These include capillary blood glucose, urine or blood ketones, serum potassium, sodium, phosphate and, very importantly, venous pH. For a suggested monitoring schedule please see Table II.

DKA is considered resolved when the blood glucose is less than 11.1 mmol/l and the serum bicarbonate above 18 mmol/l or the venous pH is greater than 7.3. Note that the clearance of serum or urine ketones takes longer to resolve than the blood glucose and the pH.

The indicators of recovery in most institutions are a pH greater than 7.3 and urine ketone-free. Evidence is accumulating to utilise point-of-care β-OHB determinations less than 1 mmol/l, on two occasions, as indicator of recovery, which seems to occur significantly earlier than urine ketone clearance.

Novel ways to monitor patients with DKA include continuous non-invasive measurement of end-tidal CO₂. This was used in two paediatric studies, which seemed to give an accurate estimate of the PCO₂ and correlated well with venous pH. Capnometry therefore allows the clinician to have a continuous, indirect indication of the acidic state of patients with DKA. The CO₂ can also be continuously measured transcutaneously.

A frequently encountered problem is to decide where to manage a patient with DKA. The ADA hospital admission guidelines for diabetes advise admission to hospital when the plasma glucose concentration is 14 mmol/l or more, the pH is less than 7.3 or the serum bicarbonate less than 15 mmol/l in the presence of moderate amounts of ketones in the blood or urine. These guidelines also suggest ICU admission in cases of severe DKA. In a survey on treatment of DKA in Denmark, it was found that in one-third of institutions DKA is routinely managed in ICU. This is also the case in the United States, where hospital policy dictates that insulin may only be administered intravenously in an ICU. In a setting with limited resources, ICU or high-care admission is frequently not an option, but a higher level of care is needed for patients with DKA due to the need for frequent monitoring and the complexity of treatment regimens. This requires a team approach of dedicated nursing and medical ward staff.

Treatment of DKA
The management of DKA is multifaceted and therefore requires a structured approach by clinicians and nurses. Numerous treatment guidelines are available in the medical literature; however, these are not always rigorously followed. In a Scottish study in an academic institution, delays in the initiation of intravenous (IV) fluid replacement and administration of insulin were seen in up to 70% of cases. Under-replacement of IV fluids and inadequate potassium replacement during...
the first 24 hours were seen in 70% of cases. These inadequacies occurred despite the availability of treatment guidelines. Every hospital managing patients with DKA should have a structured way or a so-called integrated care pathway for managing patients with DKA. This is a detailed management plan that should dictate the sequence and timing of actions, and specify by whom it should be done, in order to fulfill the goals of treatment. A recent study showed that an integrated care pathway improves key areas in the management of DKA significantly.

**Fluid replacement**

The fluid deficit is typically about 100 ml/kg body weight, which amounts to five to seven litres in the average adult patient. The deficit can be calculated using the following formulas:

\[
\text{Fluid deficit} = (0.6 \times \text{body weight in kg}) \times (\text{corrected Na}+/140)
\]

**Corrected Na+ = sNa+ + (sGlucose - 5)/3.5**

Administration of fluids alone results in a significant fall in blood glucose levels. This is mediated by recovery of the glomerular filtration rate, which declines with severe dehydration caused by the DKA. All the guidelines recently published and accessed by the author recommend the use of 0.9% NaCl solution as initial resuscitation fluid or the use of 0.45% NaCl solution if the serum sodium concentration is high. Randomised controlled trials are currently available to support the superiority of any specific fluid regimen. The use of Ringer’s lactate solution is advocated in some units based on the strong-ion theory for acidosis (Stewart’s hypothesis). Currently no definitive proof based on randomised controlled trials are available to assume that there is any benefit in using Ringer’s lactate solution instead of a saline-based regimen. Some guidelines do allow for the use of Ringer’s lactate after initial resuscitation.

Fluid resuscitation should be aggressive with the administration of 1 to 1.5 l of fluid within the first hour and thereafter 250 to 500 ml/hour. The aim is to replace 50% of the fluid deficit within the first 8 to 12 hours and the rest within the next 12 to 16 hours. Once the blood glucose drops below 14 mmol/l, it is generally advised to change the fluid administration to a dextrose-containing solution (either 5% dextrose water or 5% dextrose in 0.9% NaCl solution or 5% dextrose in 0.45% NaCl solution). In elderly patients or patients with cardiovascular, renal or liver disease, be careful for overhydration and volume overload. It is usually beneficial in these patients to monitor fluid administration invasively with a central venous line.

**Insulin therapy**

Low dose (0.1 U/kg/hour) IV administration of soluble insulin is currently the standard of care in patients with DKA. Soluble insulin (regular, lispro or aspart) should be used, but it should be noted that the synthetic insulins do not work faster than regular insulin when administered intravenously. Before commencing insulin therapy, hypokalaemia (sK+ < 3.3 mmol/l) should be excluded. Insulin should be initiated with an IV bolus of 0.1 to 0.15 U/kg followed by a continuous infusion of 0.1 U/kg/hour. Children should not receive an insulin bolus since it may increase the risk of cerebral edema. Adjust the insulin infusion rate to maintain a steady decrease in blood glucose of 3 to 5 mmol/l/hour. Once blood glucose is lower than 9 mmol/l, the infusion rate can be decreased.

After resolution of DKA, the patient can be started on a multidose insulin regimen with regular or rapid-acting insulin for prandial requirements and intermediate or long-acting insulin for basal requirements. The insulin infusion should be stopped one to two hours after the first subcutaneous insulin injection. Patients who were on insulin therapy before the onset of the DKA can be restarted on their usual insulin regimen. The usual starting dose for patients who were not on insulin before is 0.5 to 0.6 U/kg/day.

Two clinical trials have been done to assess the use of rapid acting insulin analogues subcutaneously in patients with DKA. Although these were small studies, no statistical difference in outcomes could be demonstrated between patients receiving subcutaneous rapid-acting insulin analogues and those receiving regular insulin infusions. The analogues were administered as an initial bolus of 0.3 U/kg, which was followed by 0.1 U/kg every hour until the blood glucose was less than 14 mmol/l, when the dosage was halved to 0.05 U/kg/h.

**Potassium replacement**

Total body potassium is depleted in DKA. This occurs in spite of a normal, high or a low serum potassium concentration. Volume increase during rehydration, insulin therapy and recovery of acidosis all mediate a drop in potassium concentration, which may lead to severe hypokalaemia with cardiac arrhythmias or respiratory muscle weakness. Therefore potassium needs to be replaced even if the concentration is still normal. Initiate potassium supplementation if the serum potassium is 3.3–5.3 mmol/l, and monitor it regularly.

**Bicarbonate**

The administration of bicarbonate in patients with DKA is controversial. Prospective trials have indicated that no benefit or harm is associated with the administration of bicarbonate in patients with DKA who have a pH 6.9 to 7.1. No information is available for potential benefits of bicarbonate administration in patients with a pH less than 6.9. Some published DKA guidelines recommend the use of bicarbonate if the pH is less than 7.3. Others do not recommend the use of bicarbonate at all, unless cardiogenic shock or other lactate-generating conditions are present.

**Phosphate replacement**

The total body phosphate is depleted in DKA. As in the case of potassium the serum concentration is frequently normal or high at presentation. With treatment of DKA and especially insulin administration the phosphate concentration may drop significantly. Studies evaluating the routine administration of phosphate in DKA patients did not show any benefit. However, a very low phosphate concentration may result in muscle weakness and respiratory depression and for this reason phosphate should be replaced if the serum phosphate is less than 0.33 mmol/l.

**DKA in special populations**

Although the pathophysiology of DKA is essentially the same in children, adolescents, the elderly as well as during pregnancy, each of these special populations have their specific nuances.

**Children**

Due to the inability of infants and small children to give a history of the symptoms of diabetes, DKA is often misdiagnosed at first presentation as pneumonia or bronchiolitis. The diagnosis is often made late. At diagnosis patients are frequently severely dehydrated, have severe acidosis and are often unconscious. Children require a more precise calculation and replacement of fluid losses because of changes in
The development of DKA. The perinatal mortality related to DKA is between 50% and 80%.

During pregnancy not only the mother is significantly affected by the development of DKA. The perinatal mortality related to DKA is between 9 and 35%. DKA during pregnancy results in reduced oxygenation of the feto-placental unit due to reduced uterine blood flow and a left shift in the haemoglobin dissociation curve (increased affinity of haemoglobin for oxygen). During DKA foetal distress is frequently observed, but intervention for foetal compromise should be delayed until the mother is properly resuscitated, because this frequently reverses foetal distress.

### Adolescents

The major problem in this patient group is neglect on the part of patients to take insulin with serious lapses in patient adherence to treatment. These patients need to be seen in conjunction with their families, and long-term psychological support may be needed to prevent repeated DKA episodes. In this patient group, 5% of patients are responsible for more than 25% of DKA admissions. Adolescents

### The elderly

Comorbid conditions play an important role in elderly patients. It predisposes them to DKA and a poorer outcome of DKA. Important precipitating conditions that need to be considered in elderly patients with DKA are myocardial infarctions, stroke and infections. In a UK study females older than 59 years of age were identified as a high-risk group for recurrent DKA due to other chronic diseases complicating the diabetes.

### During pregnancy

During pregnancy not only the mother is significantly affected by the development of DKA. The perinatal mortality related to DKA is between 50% and 80%. During pregnancy not only the mother is significantly affected by the development of DKA. The perinatal mortality related to DKA is between 50% and 80%.

### Table III: Summary of management of DKA in adults

<table>
<thead>
<tr>
<th>Timing</th>
<th>IV fluids</th>
<th>Insulin</th>
<th>Electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission</strong></td>
<td>0.9% NaCl: 1 to 1.5 litre in the first hour (infusion rate: 15-20 ml/kg)</td>
<td>IV bolus: Regular insulin 0.1–0.15 IU/kg followed by a continuous infusion at a rate of 0.1 IU/kg per hour</td>
<td>Bicarbonate (Controversial) If the pH &lt; 7.0; 56 mmol/l NaHCO₃ in 200 ml 0.45% saline over one hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually prepared as follows: 20 IU in 200 ml 0.9% saline (0.1 IU/ml)</td>
<td>If the pH &lt; 6.9: 100 mmol/l NaHCO₃ in 400 ml 0.45% saline over one hour</td>
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<td></td>
<td></td>
<td>Thus for an 80 kg person: 8 IU/h = 80 ml/h or 80 microdrops/min</td>
<td>This can be repeated two-hourly</td>
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<td></td>
<td></td>
<td>Reassess blood glucose</td>
<td>Potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase the insulin infusion rate if the blood glucose concentration does not decrease by 3 to 4 mmol/l/h</td>
<td>Always check K⁺ concentration before commencing with insulin administration.</td>
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<tr>
<td></td>
<td></td>
<td>Adjust infusion rate two-hourly based on blood glucose as follows:</td>
<td>• If sK⁺ &gt; 5.0 mmol/l no K⁺ supplement but check q two-hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• s Glucose: &lt; 5.6 mmol/l decrease by 10 ml/h and give 25 ml of 50% dextrose IV</td>
<td>• If sK⁺ 3.0 – 5.0 mmol/l add 20 mmol in each litre of IV fluid in order to maintain the sK⁺ concentration between 4.0–5.0 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• s Glucose: 5.6–8.9 mmol/l decrease by 10 ml/h (1 IU/h)</td>
<td>If sK⁺ &lt; 3.0 mmol/l add 40 mmol to the initial IV fluid (withhold insulin until K⁺ &gt; 3.0 mmol/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• s Glucose: 9–12.2 mmol/l no change</td>
<td>Phosphate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• s Glucose: 12.3–15.6 mmol/l increase by 10 ml/h (1 IU/h)</td>
<td>Replacement only necessary if PO concentration is &lt; 0.33 mmol/l. Replace with potassium phosphate solution IV 14 mmol (10 ml) in 1L rehydration fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• s Glucose: &gt; 15.6 mmol/l increase by 10 ml/h and give a bolus of regular insulin of 8 U IV</td>
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<td></td>
<td></td>
<td>When the patient is able to eat, give meal-related boluses of regular insulin (usually 1 IU per 15 g carbohydrate in meal), in addition to the continuous IV insulin infusion</td>
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<td></td>
<td></td>
<td>Change to 5% dextrose or 5% dextrose in 0.45% NaCl solution</td>
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<tr>
<td><strong>After 1 hour</strong></td>
<td>Reassess: Hydration status hourly sNa⁺ concentration</td>
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<tr>
<td></td>
<td>Continue with 0.9% NaCl if sNa is normal or low: 250–500 ml/h (4–14 ml/kg depending on the hydration status)</td>
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<tr>
<td></td>
<td>If sNa⁺ is elevated change to 0.45% NaCl</td>
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<td></td>
<td>Replace half the fluid deficit in the first 12 hours (serum osmolality should not change &gt; 0.3 Osmol/kg</td>
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</tbody>
</table>

References