Diabetic ketoacidosis: principles of management

Diabetic ketoacidosis has a mortality of up to 14% in the UK, which could be attributed to varied treatment policies and a lack of a general consensus statement on its management. This article provides comprehensive guidelines for management of adult patients in diabetic ketoacidosis.

Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes. This hyperglycaemic emergency continues to be an important cause of morbidity and mortality despite major advances in understanding its pathogenesis. Unpublished data from the Intensive Care National Audit and Research Centre reports an inhospital mortality resulting from DKA of up to 14%.

Definition

The three cardinal biochemical features of DKA are hyperglycaemia, ketonaemia and metabolic acidosis. Alberti's definition describes severe uncontrolled diabetes requiring emergency treatment with insulin and intravenous fluids and with a blood ketone body level greater than 5 mmol/litre. *Table 1* provides an empirical classification of DKA and hyperglycaemic hyperosmolar state.

Precipitating factors

The three most common precipitants for DKA are:

1. Infection (30–50%): pneumonia, urinary tract infections (Kitabchi et al 2001), sepsis, gastroenteritis
2. Inadequate insulin treatment (20–40%): omission, inadequate treatment, pump failure
3. New-onset diabetes (20–30%).

Table 2 lists the other precipitating factors of DKA (Kitabchi et al, 2004). In 2–10% of patients, no precipitating cause is identified (Magee and Bankim, 2001).

Table 1. Diagnostic criteria for diabetic ketoacidosis and hyperglycaemic hyperosmolar state

	Diabetic ketoacidosis			Hyperglycaemic hyperosmolar state
	Mild	Moderate	Severe	
Plasma glucose (mmol/litre)	>14	>14	>14	>35
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mmol/litre)	15–18	10 to<15	<10>	15
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	<12
Alteration in sensorial or mental obtundation	Alert	Alert/ drowsy	Stupor/ coma	Stupor/ coma

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Pathophysiology

The basic mechanism for the development of DKA is a reduction in the effective insulin concentration and increased counter-regulatory (catabolic or stress) hormones like glucagon, catecholamines, cortisol and growth hormone (*Figure 1, Table 3*). This insulin deficiency can be absolute or relative. This deficiency of insulin results in a decrease in the net effective insulin concentration which in turn affects carbohydrate, lipid and protein metabolism (Miles et al, 1980).

Clinical features

The initial approach to a diagnosis of DKA consists of a rapid, relevant history (including previous episodes of ketoacidosis, if any, and trying to elucidate a possible precipitating factor) and a thorough physical examination. Cardinal features of DKA are polyuria and polydipsia.

Table 2. Precipitating factors for diabetic ketoacidosis

Infection
Inadequate insulin treatment
New-onset diabetes
Cerebrovascular accident
Myocardial infarction
Acute pancreatitis
Intestinal obstruction
Alcohol intoxication/ abuse
Renal failure (+/- peritoneal dialysis)
Severe burns
Drugs such as thiazide diuretics, steroids, and sympathomimetics

Generalized weakness and lethargy is common. The general appearance of patients with DKA is one of fatigue and dehydration (Charfen and Fernandez-Frackelton, 2005).

Airway

Patency of the airway may be compromised because of an alteration in the level of consciousness.

Breathing

The patient may be tachypnoeic with Kussmaul respiration. A fruity odour indicating exhaled acetone may be present.

Circulation

Tachycardia and hypotension may be present as a result of volume depletion, sepsis or both. Signs of dehydration including poor urine output, loss of skin turgor, dry mucous membranes and impaired capillary refill should be looked out for. Accompanying co-morbidities, especially in the elderly, may precipitate cardiogenic shock. The patient may be hypothermic or normothermic despite accompanying infection (Kitabchi et al, 2004).

Mental status

This varies from full alertness to comatose. Less than 20% of patients with DKA are admitted comatose (Kitabchi et al, 2001). Coexisting causes of coma such as head injury, drug overdose and stroke should be excluded. A complete neurological assessment of patients with altered sensorium and localizing signs should be carried out.

Careful physical examination includes abdominal palpation to rule out localizing tenderness as an intra-abdominal pathology may be the precipitating factor for DKA. A succussion splash may be evident on abdominal examination as a result of gastric stasis. Sinuses, oral cavity and ears should be examined to rule out infection. Skin over the back and peripheries should be examined for abscess, cellulitis or decubitus ulcers. Rectal examination should be carried out to exclude perianal abscess or occult gastrointestinal haemorrhage.

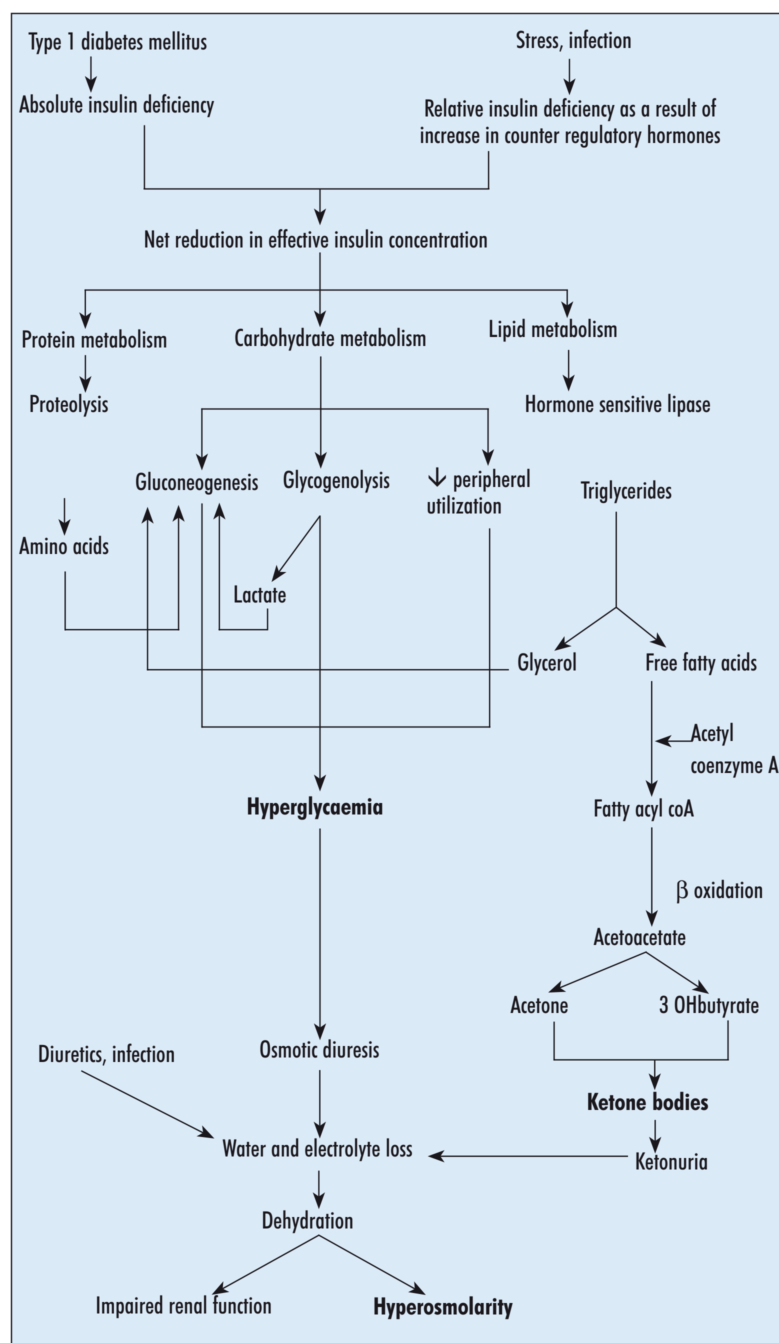

Figure 1. Pathophysiology of diabetic ketoacidosis. Modified from Kitabchi et al (2001).

Diagnostic investigations

The initial laboratory evaluation of a patient with suspected DKA should include:

1. Arterial blood gases
2. Haematology and biochemistry: full blood count, coagulation profile, renal and liver function tests, toxicology screen, amylase, glucose, osmolality, ketones, C-reactive protein and troponin T. Serum electrolytes including phosphate and magnesium levels
3. Urinanalysis: dipstick test for protein, nitrites, ketones, β-human chorionic gonadotropin (should be performed on all females of childbearing age) and leucocytes
4. Bacterial cultures of urine, blood and sputum
5. 12-lead electrocardiogram and then continuous electrocardiogram monitoring especially in patients with electrolyte imbalance
6. Chest X-ray.

Other laboratory evaluation should be based upon findings on physical examination, acute deterioration of condition and failure to respond to management.

Pitfalls of diagnosis

DKA has been mistaken for other conditions like pulmonary embolism, alcohol intoxication and panic attacks leading to delayed treatment with disastrous consequences. Potential pitfalls in the diagnosis and management of DKA may include:

1. Normoglycaemia may occur in patients who took insulin before presentation or have impaired gluco-

Table 3. Typical total body deficits of water and electrolytes in diabetic ketoacidosis

Total water	5–11 litres
Na+	7–10 mmol/kg
Cl-	3–5 mmol/kg
K+	3–5 mmol/kg
PO4	5–7 mmol/kg
Mg2+	0.5–1 mmol/kg
Ca2+	0.5–1 mmol/kg

neogenesis caused by liver failure or alcohol abuse (Magee and Bankim, 2001)
2. Euglycaemic DKA has been reported in up to 18% of cases (Cydulka and Jonathon, 2002)
3. Leucocytosis may be secondary to haemoconcentration, infection, ketosis, myocardial infarction or pancreatitis (Charfen and Fernandez-Frackelton, 2005)
4. Pseudohyponatraemia may be present as a result of lipid dilution of the serum (Kitabchi et al, 2001, 2004)
5. Plasma potassium concentration may be falsely elevated despite severe total body depletion (Assadi et al, 1985; Gerard and Khayam-Bashi, 1985)
6. Plasma creatinine concentration may be falsely elevated as a result of acetoacetate interference
7. Ketostix: may show negative or trace result when alcohol ketoacidosis and lactic acidosis coexist with diabetic acidosis
8. Plasma amylase is elevated in most patients with DKA. Hyperamylasaemia may be the result of extra pancreatic secretion (Vinicor et al, 1979)
9. High anion gap: the anion gap may be increased as a result of conditions like lactic acidosis, salicylate, methanol and ethylene glycol poisoning, and alcoholic ketoacidosis. Rarely, a well-hydrated patient with DKA may have a pure hyperchloraemic acidosis and no anion gap (Cydulka and Jonathon, 2002).

Management of DKA

The management of DKA should include intravenous fluid hydration, switching off ketosis with insulin administration, electrolyte replacement and identifying and treating precipitating events.

Table 4. Useful formulae in diabetic ketoacidosis

Correction of serum sodium	Add 1.6 mEq/litre to the sodium for every 5.5 mmol of glucose above the normal
Serum osmolality (mOsm/kg H_2O)	2 (Na + K) + glucose + urea
Effective serum osmolality (mOsm/kg H_2O)	2 (Na + K) + glucose
Total body water deficit (litres)	0.6 x weight (kg) x (1 – 140 / serum sodium)
Anion gap	(Na – (Cl + HCO3))

Intravenous fluids

Fluid replacement alone may decrease serum glucose concentration by as much as 23% through increased renal perfusion and loss of glucose in the urine (West et al, 1986). The total body water (TBW) deficit is usually 5–11 litres and can be calculated by the formula in *Table 4.*

The algorithm in *Figure 2* is suggested for fluid management in patients with DKA. The aim of rehydration therapy is to correct the TBW deficit over 24 hours: 50% of this deficit should be corrected within the first 8 hours and the remaining 50% over the next 16 hours (Charfen and Fernandez-Frackelton, 2005). The initial fluid of choice is 0.9% normal saline in the first hour. Subsequent choice for fluid replacement depends on the patient's hydration status, serum electrolyte levels and urine output.

Special care should be taken to avoid overhydration in children, patients with cardiac or renal compromise, and older patients with DKA. The lung sounds and oxygenation should be assessed frequently. Mental status should be assessed and osmolarity should be calculated to avoid cerebral oedema.

Although all authors agree that fluid administration is essential in DKA, there is no uniformly accepted formula for administration. Many authors believe that the calculation of TBW deficit and other losses should be kept simple. Most of this debate refers to paediatric patients in DKA who tend to tolerate fluid overload poorly as compared to adults. The authors believe that one cannot be dogmatic about estimation and subsequent correction of fluid deficit. They have modified the protocol set by the American Diabetes Association (*Figure 3*) and advocate fluid rehydration based on frequent reassessment of hydration status, invasive monitoring and response to rehydration therapy. This is a guideline for estimation of fluid rehydration and not a substitute for clinical judgment.

Insulin

Insulin therapy is secondary to intravenous fluid replacement and should be withheld initially in patients with hypotension and hypokalaemia. Insulin therapy should not be initiated until serum potassium is over 3.5 mmol/litre (Kitabchi et al, 2004). The route of administration of insulin has been debated. Intravenous insulin causes a greater decline in blood glucose and ketone body levels in the first 2 hours of therapy than intramuscular or subcutaneous insulin. Furthermore, the dehydration and shock state of patients in DKA leads to erratic and unpredictable absorption of intramuscular and subcutaneous insulin.

Some authors recommend an initial intravenous bolus of regular insulin 0.10–0.15 U/kg, but there are no data to support clinical benefit. Because insulin has a plasma half life of 3–5 minutes, intermittent intravenous injections can lead to unpredictable and fluctuating plasma insulin concentrations. The algorithm in *Figure 3* is suggested for insulin administration for patients in DKA. When reviewing the progress of treatment, it is important to consider a failure in insulin delivery if blood glucose fails to drop

appropriately. In some patients, persistent hyperglycaemia may be the result of severe insulin resistance which necessitates an increase in the insulin dose. However, because the primary mechanism for lowering blood glucose in the early stages of treatment is urinary glucose disposal rather than insulin stimulated glucose consumption, the problem may simply reflect inadequate replacement of intravascular volume, in which case insulin rates may not need to be increased. Studies show that replacement of fluid and electrolytes alone may diminish insulin resistance by decreasing the levels of counter regulatory hormones and hyperglycaemia as well as by decreasing the osmolarity, making the cells more responsive to insulin (Waldhausl et al, 1979; Bratusch-Marrain et al, 1985).

Some recommend the use of very low-dose insulin infusion (0.05 U/kg/hr) and a project comparing the efficacy of a regimen using 0.05 U/kg/hr *vs* 0.1 U/kg/hr has been proposed by the British Society of Paediatric Endocrinology and Diabetes (BSPED).

Blood glucose should not be allowed to fall below 11–14 mmol/litre in the first 24 hours of therapy or until ketoacidosis (pH > 7.3, HCO_3 > 18 and anion gap ≤ 12) has resolved (Lebovitz, 1995). Once the serum glucose is 11–14 mmol/litre and ketoacidosis has resolved, switch to a sliding scale regimen. Post hyperglycaemic management is discussed later in this article.

Potassium

Potassium is the major electrolyte lost in DKA. Despite total body potassium depletion, mild-to-moderate hyperkalaemia is still common. Hypokalaemia may result during treatment of DKA as a result of insulin-mediated intracellular movement of potassium, volume expansion, resolution of acidaemia and ongoing potassium loss through osmotic diuresis. Before potassium administration adequate urine output must be ensured.

Measure serum potassium on admission. No potassium is required in the first hour unless serum potassium is less than 3.5 mmol/litre on admission. For subsequent administration, see *Table 5*.

Review serum potassium 2-hourly and replace accordingly. Continuous ECG monitoring is recommended during potassium therapy.

Bicarbonate

Most studies do not recommend the use of bicarbonate in DKA although the number of patients with a pH <6.9 is low in these studies (Green et al, 1998; Viallou et al, 1999). No prospective randomized studies concerning the use of bicarbonate in DKA with arterial pH values <6.9 have been reported. The potential disadvantages of bicarbonate therapy are:

1. For each 100 mEq of bicarbonate given 2.24 litres of carbon dioxide has to be exhaled which is equivalent to 10 minutes of normal production
2. Carbon dioxide enters the cells freely and therefore increases intracellular acidosis

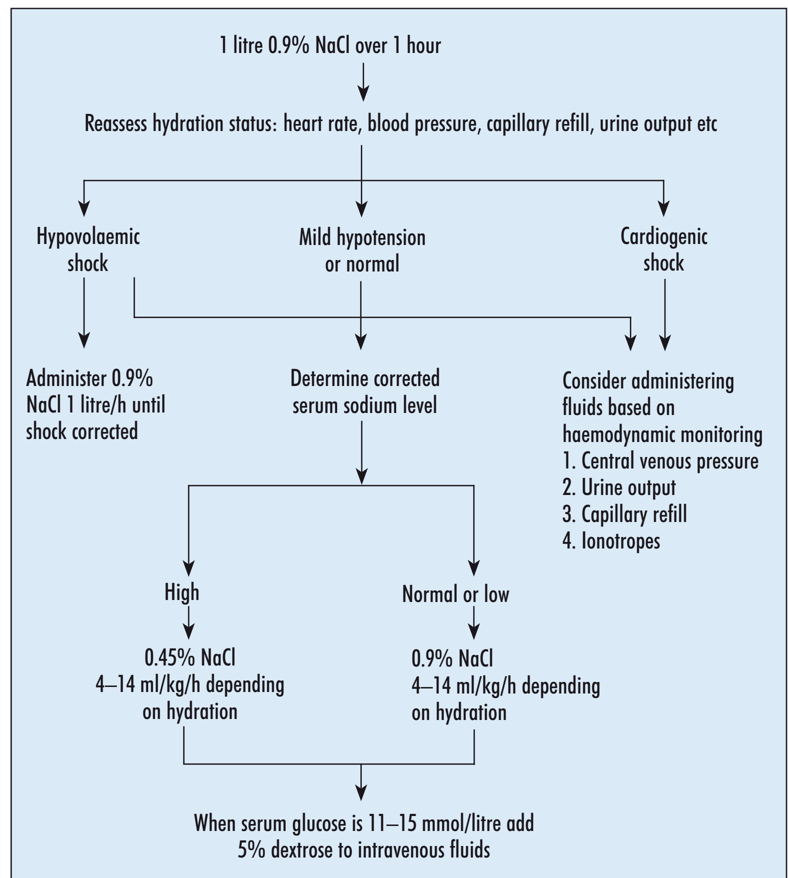

Figure 2. Fluid management in diabetic ketoacidosis. Modified from Kitabchi et al (2001).

3. Bicarbonate is accompanied by sodium ions and therefore increases osmolality of extracellular fluid
4. Bicarbonate will worsen hypokalaemia, especially with early rehydration and insulin
5. Paradoxical CSF acidosis
6. Acidosis causes shift of oxyhaemoglobin curve to the right, as a compensation 2,3-diphosphoglycerate (DPG) decreases to manage normal position of the curve. Rapid correction of bicarbonate will shift the acidosis to normal but 2,3 DPG will take 2–3 days to recover and tissue oxygenation can be impaired

Figure 3. Insulin management in diabetic ketoacidosis.

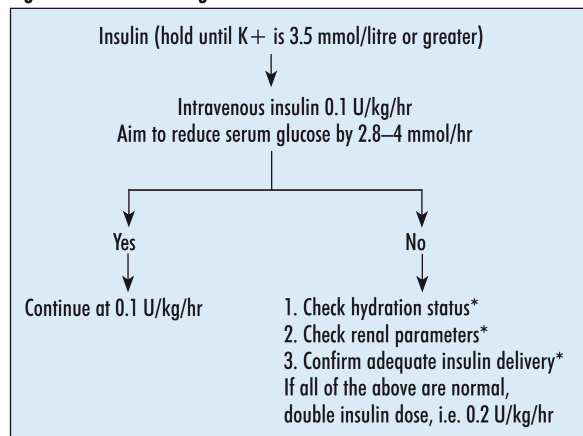

Table 5. Serum potassium administration in diabetic ketoacidosis

Serum potassium (mmol/litre)	KCl to be added
< 3.5	40 mmol/litre (Hold insulin until K+ > 3.5)
3.5–5.5	20 mmol/litre
>5.5	Not required

7. 8.4% solution of sodium bicarbonate is hypertonic and extremely irritant and can cause extensive local necrosis if administered peripherally.

If pH remains <6.9 despite adequate volume resuscitation, insulin therapy, adequate urine output, absence of sepsis and no other identifiable cause of acidosis, then sodium bicarbonate can be given as a 1.4% isotonic solution (usual dose is 44–88 mEq sodium bicarbonate) over 30–60 minutes with 10–20 mmol of added potassium (if serum potassium is <5.5 mmol/litre).

Phosphate

Hypophosphataemia is a potential complication of insulin therapy in DKA in addition to losses resulting from osmotic diuresis. Although routine phosphate replacement is unnecessary in DKA, replacement should be given with serum phosphate concentrations <0.35 mmol/litre and to patients with moderate hypophosphataemia and concomitant hypoxia, anaemia or cardiorespiratory compromise (Kreisberg, 1977).

If phosphate replacement is needed, 20–30 mEq/litre potassium phosphate can be added to replacement fluids and given over several hours. Serum calcium levels should be monitored during therapy with phosphate to avoid hypocalcaemia.

Magnesium

As outlined in *Table 3*, a serum deficit of 0.5–1 mmol/litre of magnesium usually exists in DKA. Use of diuretics by these patients adds to the magnesium loss. Magnesium may need replacing especially if symptoms of hypomagnesaemia develop. Patients are usually symptomatic at serum levels of 0.5 mmol/litre or lower (Tso and Barish, 1992). If the level is below normal (0.74 mmol/litre) and symptoms are present, administration of magnesium should be considered. Magnesium sulphate 20 mmol in 100 ml of 0.9 % normal saline can be administered over 1 hour and repeated as necessary.

Other measures

1. Continuous ECG monitoring
2. A nasogastric tube should be inserted if the patient has an impaired level of consciousness
3. Urinary catheterization
4. Central venous access may be needed in elderly patients with heart failure and for potassium supplementation
5. Antibiotic therapy if there is evidence of infection. White cell count may be spuriously raised in DKA and does not confirm infection. History, examination, pyrexia and elevated C-reactive protein are more helpful markers (Wallace and Matthews, 2004)
6. Thromboembolic prophylaxis.

Immediate post hyperglycaemic care

Magee and Bankim (2001) have shown that using 7 hours of continuous insulin infusion after normoglycaemia would allow for complete resolution of ketosis. Once ketosis has resolved, the patient should be given his or her first dose of subcutaneous insulin. It is important that the insulin drip is continued after the initiation of subcutaneous insulin, because hyperglycaemia may recur rapidly with interruptions in insulin administration. The BSPED recommends that insulin be continued for 60 minutes (if using soluble or long-acting insulin) or 10 minutes (if using Novorapid (Novo Nordisk, Denmark) or Humalog (Eli Lilly and Company, USA)) after the first subcutaneous injection to avoid rebound hyperglycaemia.

When the patient is able to eat, a multiple daily injection schedule may be established. Patients known to have diabetes may be given insulin at the dose they were receiving before the onset of DKA. In patients with newly diagnosed diabetes, the initial total insulin dose should be 0.6 U/kg/day, divided into at least three doses in a mixed regimen including short- and long-acting insulin, until an optimal dose is established.

Complications of therapy

Most complications of DKA relate to treatment. The most common complications include hypoglycaemia, hypokalaemia, recurrent hyperglycaemia and hyperchloraemia (Oh et al, 1981; Adrogue et al, 1982). Less common complications include cerebral oedema, fluid overload, acute respiratory distress syndrome, thromboembolism and acute gastric dilation. Cerebral oedema is discussed as it is a fatal complication of DKA especially in children.

Cerebral oedema

The mortality rate from cerebral oedema according to different series has varied widely, with reports between 24% and 90% (Edge et al, 2001). Clinically apparent cerebral oedema develops in 1–2% of ketoacidotic diabetic children (Duck and Kohler, 1981; Glaser et al, 2001), although subclinical oedema demonstrable by computed tomography scanning or raised CSF pressure probably occurs in most cases during treatment (Dorman et al, 1984) and indeed is likely to be present even before treatment begins (Krane et al, 1985; Durr et al, 1992).

A national UK case-control study through the British Paediatric Surveillance Unit (Edge et al, 2006) identified risk factors which are strong predictors of cerebral oedema. These include degree of acidosis on admission, raised plasma urea concentration, low sodium and high potassium concentration, overzealous fluid administration within the first 3–4 hours of initiation of treatment, insulin administration within the first hour of fluid treatment and larger doses of insulin during the first 2 hours of treatment.

Preventative measures that might decrease the risk of cerebral oedema in high-risk patients are:

1. Gradual replacement of sodium and water deficits in patients who are hyperosmolar (maximal reduction in osmolality of 3 mOsm/kg H_2O/hr)
2. Avoid bicarbonate replacement unless absolutely vital
3. The addition of dextrose to the intravenous fluid therapy once blood glucose reaches 14 mmol/litre.

Once developed, cerebral oedema can be treated with mannitol 1–2 g/kg over 15 minutes to be commenced within 5–10 minutes of neurological deterioration for maximum effect. The role of dexamethasone and diuretics has not been established.

Conclusions

DKA is a life-threatening condition which requires early diagnosis and immediate management. The key focus of management is fluid rehydration and not insulin administration, with an aim to achieve rehydration at 24 hours, normoglycaemia at 24–48 hours and to continue insulin until ketosis resolves. Judicious fluid management and insulin administration can reduce the incidence of cerebral oedema, a potentially fatal complication of DKA. **BJHM**

Figures 1 *and* 2 *are modified from Kitabchi et al (2001) by kind permission of the American Diabetic Association.*

Conflict of interest: none.

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KEY POINTS

- Diabetic ketoacidosis, a life-threatening condition requiring immediate hospitalization and treatment, is often overlooked. Early recognition is vital as minor delays in diagnosis and initiation of treatment can affect survival.
- Early diagnosis, fluid rehydration, continuous low-dose insulin administration and electrolyte replacement are the pillars of management.
- The key focus of diabetic ketoacidosis management is fluid rehydration and not insulin administration, a fact commonly ignored in practice.
- Insulin should be administered intravenously as a low-dose continuous infusion.
- The aim is to achieve adequate rehydration at 24 hours, normoglycaemia at 24–48 hours and continue insulin until ketosis resolves.
- Bicarbonate replacement has no documented benefit in diabetic ketoacidosis unless there is no identifiable cause of acidosis. Replacement of electrolytes such as potassium, magnesium and phosphate is indicated in symptomatic patients.
- Most complications of diabetic ketoacidosis are related to treatment and the more fatal ones such as cerebral oedema are rare. Nevertheless caution should be exercised as regards fluid administration in high-risk patients such as children, elderly and those with cardiovascular and renal disease.