# Diabetic ketoacidosis

Claire Preedy and William English
Correspondence Email: englishwilliam@hotmail.com

**Diabetic ketoacidosis**

## DEFINITION

Diabetes ketoacidosis (DKA) is a medical emergency. It is classified by the triad of:

- Ketonaemia (3mmol.L$^{-1}$ and over) or significant ketonuria (more than 2+ on standard urine sticks),

- Blood glucose over 11mmol.L$^{-1}$ or known diabetes mellitus,

- Bicarbonate (HCO3$^{-}$) below 15mmol.L$^{-1}$ and/or venous pH less than 7.3.

The main differential diagnosis is hyperosmolar hyperglycaemic syndrome, alternatively known as hyperosmolar non-ketotic syndrome (HONK). Despite significant overlaps between the two conditions, this article will only address DKA.

As there are important differences between the management of the adult and paediatric populations, the treatment of each group will be discussed separately.

## EPIDEMIOLOGY

DKA primarily occurs in patients with type 1 diabetes mellitus, but is being recognised in type 2 diabetes patients.[2] The true incidence is difficult to establish, but population based studies estimate between 4.6 and 8 episodes per 1,000 patients with diabetes.[3]

DKA may be the first presentation of diabetes, or may follow a precipitating event. This is most commonly infection, although in a large number of cases no identifiable cause can be found (Table 1).

## MORTALITY AND MORBIDITY

Better understanding of the pathophysiology of DKA, with close monitoring and controlled correction of electrolytes has seen a reduction in the overall mortality of DKA in the last 20 years from 7.96% to 0.67%.[4] The mortality is still high in non-hospitalised patients and in the developing world.

The most common cause of mortality in DKA is cerebral oedema, particularly in children and adolescents. In the adult population, the main causes of mortality

**Table 1.** *Common precipitating events of DKA.*

| Precipitant | Occurrence (%) |
|---|---|
| Infections (commonly urinary tract) | 30 |
| Non-compliance with treatment | 15 |
| New diagnosis of type 1 diabetes | 5-15 |
| Other stresses (MI, alcohol, pancreatitis, drugs) | 5 |
| No cause found | up to 40 |

include severe hypokalaemia, adult respiratory distress syndrome, and co-morbid states such as pneumonia, acute myocardial infarction and sepsis.[5]

## PATHOPHYSIOLOGY

Diabetic ketoacidosis is a complex metabolic disorder characterised by hyperglycaemia, acidosis and ketonaemia. It usually results from an absolute or relative lack of insulin and is complicated by a corresponding rise in counter-regulatory hormones - glucagon, cortisol, growth hormone and the catecholamines. This hormone imbalance reduces the uptake of glucose by peripheral tissues and increases hepatic gluconeogenesis and glycogenolysis, resulting in severe hyperglycaemia. Enhanced lipolysis increases the breakdown of triglycerides into free fatty acids. Large quantities of ketones are then formed by the β-oxidation of the free fatty acids. Ketones include acetone, 3-β-hydroxybutyrate and acetoacetate. The predominant ketone in DKA is 3-β-hydroxybutyrate.

The secondary consequences of these primary derangements include metabolic acidosis and an osmotic diuresis. Metabolic acidosis is created by the production of H$^{+}$ ions by the dissociation of ketoacids. The accumulation of ketoacids leads to an elevated anion gap, which is a key feature of DKA.

There are several mechanisms for dehydration in DKA. These include osmotic diuresis, vomiting and eventually reduction in oral intake due to reduced level of consciousness. Initially, as the blood sugar rises, there is a shift of fluid from the intracellular to the extracellular compartment with subsequent dilution. Once the

**Summary**

Diabetic ketoacidosis remains a frequent and life-threatening complication of type 1 diabetes. Recent national (UK) guidelines have seen some changes in the management of the condition, and this article reflects the current best practice.[1]

*Claire Preedy*
Anaesthesia trainee

*William English*
Consultant in Intensive Care
Royal Cornwall Hospitals
NHS Trust
Truro
UK

blood sugar levels exceed the renal threshold for glucose of around 12mmol.L$^{-1}$, glycosuria occurs. This results in an osmotic diuresis, with a loss of water from the extracellular compartment. Electrolyte shifts and depletion are in part due to this osmotic diuresis. As well as losing glucose and water in the urine, there will be urinary loss of ketones, sodium, potassium and phosphates. At presentation these patients are often severely dehydrated with marked serum electrolyte disturbances.

## CLINICAL FEATURES

There is a wide spectrum of severity of illness in patients presenting with DKA. Classically patients present with a history of thirst, polyuria and polydipsia, although these are not invariably present. Diabetes mellitus may have been previously undiagnosed.

*Other symptoms may include:*

- Weakness and lethargy
- Nausea and vomiting
- Abdominal pain
- Weight loss.

*Common general physical signs are:*

- Evidence of dehydration
- Tachycardia and hypotension
- Kussmaul respiration (deep, laboured respirations to provide respiratory compensation for metabolic acidosis)
- Ketotic breath (fruity acetone smell due to exhaled ketones)
- Temperature is usually normal or low, even in the presence of an underlying infection[6]
- Altered consciousness and confusion.

## INVESTIGATIONS

Initial investigations aim to confirm the diagnosis, estimate the severity of the DKA and identify the underlying cause.

### Blood glucose

Usually blood glucose is grossly elevated at presentation. Rarely it may be normal or only moderately raised if there has been partial treatment of DKA prior to presentation, as this may reduce the blood glucose but not correct the acidaemia. This is known as euglycaemic diabetic ketoacidosis.

Capillary and laboratory blood glucose should be taken on presentation. It is important to remember that 'near patient' testing of blood glucose may be grossly inaccurate with very high concentrations of glucose. Blood glucose should then be checked hourly. Laboratory testing is only necessary until levels are back within the range of the near patient testing devices.

### Ketones

In some settings, portable ketone meters now allow bedside measurement of blood ketones (3-beta-hydroxybutyrate). The resolution of DKA depends on the suppression of ketonaemia, therefore measurement of blood ketones now represents best practice in monitoring response to treatment.

Urine ketones can be measured on urine dipstick.

### Serum urea and electrolytes

These should be measured in the laboratory initially and ideally should then be monitored hourly using venous or arterial blood gas sampling.

### Sodium

As discussed above, hyperglycaemia causes a dilutional hyponatraemia. The measured serum sodium level can be corrected by adding 1.6mmol.L$^{-1}$ for each 5.5mmol.L$^{-1}$ elevation of glucose over 5.5mmol.L$^{-1}$. One correction formula is:

$$\text{Corrected Na}^+ = \text{Measured Na}^+ + 0.4 \times ([\text{Plasma glucose (mmol.L}^{-1})] - 5.5)$$

Alternatively visit: http://www.strs.nhs.uk/resources/pdf/guidelines/correctedNA.pdf

### Potassium

In DKA there is a total body deficit of potassium. However, initial serum levels may be within the normal range or elevated because of acidosis and dehydration. Serum levels must be checked regularly because correction of the acidosis and administration of insulin can result in a precipitous drop in serum potassium, via intracellular movement of potassium.

### Urea and creatinine

Renal impairment may be present at presentation. Elevated acetoacetate levels may cause a falsely elevated creatinine level if the calorimetric method is used to measure the serum creatinine.

### Serum osmolality

This can be calculated as: (2 x Na) + glucose + urea. If a patient in DKA is comatose with an osmolality less than 330mosm.kg$^{-1}$ then other sources for coma should be sought.

### Venous or arterial blood gases

Either venous or arterial blood gas measurement is useful at presentation, 60 minutes, 2 hours and 2 hourly thereafter, until at least 6 hours from commencing treatment.

An elevated anion gap is a key feature of DKA. Anion gap is calculated as:

$$(\text{Serum Na}^+ + \text{serum K}^+) - (\text{serum HCO}_3^- + \text{serum Cl}^-)$$
$$\text{Normal value: 8-12mmol.L}^{-1}$$

### Full blood count

An increased white blood cell count in the range 10-15 x10$^9$.L$^{-1}$ is characteristic of DKA and is not indicative of infection. However a count above 25x10$^9$.L$^{-1}$ should raise concern that an infection is present.

### Amylase

Amylase is often raised in the absence of pancreatitis. This may cause diagnostic confusion, especially in the presence of abdominal pain.

### Other investigations

Other investigations are necessary to aid diagnosis of any underlying cause and to monitor for complications. They include:

- Blood cultures

- ECG

- Chest Xray

- Mid-stream urine.

Children should be weighed to guide fluid and drug therapy. If this is not possible an estimated weight should be calculated.

Excellent comprehensive guidelines and a pathway poster are available at **www.diabetes.org.uk.** Follow the links: 'About us' > 'Our policy views' > 'Care recommendations' > 'The management of diabetic ketoacidosis in adults'

### MANAGEMENT OF ADULTS IN DIABETIC KETOACIDOSIS

### Initial assessment and resuscitation

Patients with DKA may be severely unwell and comatose. The initial approach requires a rapid assessment of Airway, Breathing, Circulation and Disability, administration of oxygen and confirmation of the diagnosis. Intravenous access should be established as soon as possible, blood tests and blood cultures taken, and treatment started with fluid initially and insulin later (see below). A full clinical examination is mandatory, followed by further investigations as above. Precipitating causes should be considered and treated as appropriate.

The focus of treatment of DKA is now on the underlying metabolic abnormality (ketonaemia), which simplifies the treatment of those who present with euglycaemic diabetic ketoacidosis.

The basic principles of DKA management are:

- Rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids,

- Gradual rehydration and restoration of depleted electrolytes,

- Insulin to reverse ketosis and hyperglycaemia,

- Careful and regular monitoring of clinical signs and laboratory tests to detect and treat complications.

### Fluid administration and deficits

The most important initial treatment in DKA is appropriate fluid replacement followed by insulin administration. The main aims for fluid replacement are:

- Restoration of circulating volume,

- Clearance of ketones,

- Correction of electrolyte imbalance.

Typical Deficits in DKA are:

- Water            $100ml.kg^{-1}$

- Sodium          $7\text{-}10mmol.kg^{-1}$

- Chloride        $3\text{-}5mmol.kg^{-1}$

- Potassium      $3\text{-}5mmol.kg^{-1}$

So a 70kg adult presenting with DKA may be up to 7 litres in deficit.

The aim of the first few litres of fluid is to correct hypotension, replenish the intravascular deficit and counteract the effects of the osmotic diuresis, with correction of electrolyte disturbance.

Initially fluid therapy is aimed at rapid restoration of intravascular volume. This is done by judicious fluid boluses of 0.9% saline. Patients in cardiogenic or septic shock will require vasoactive drugs and haemodynamic monitoring. As a guide to fluid replacement, after initial resuscitation with 0.9% saline, a typical fluid regime is suggested in Table 2.

**Table 2.** *Typical fluid replacement regime.*

| Fluid | Volume |
| --- | --- |
| 0.9% sodium chloride | 1000ml over 1st hour |
| 0.9% sodium chloride with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride with potassium chloride | 1000ml over next 6 hours |

It is extremely important to remember that this is a guide only. Fluid therapy should be judged by repeated clinical assessment, including blood pressure, urine output and mental status. Special care is required in vulnerable patient groups, such as the elderly, pregnant women, those aged 18-25 yrs (see cerebral oedema), patients with heart or kidney failure and any patient with other serious co-morbidities.

### 0.9% saline or Hartmann's solution for resuscitation?

There has been much recent debate about the relative merits of these two solutions.[7,8,9] 0.9% saline can cause a hyperchloraemic metabolic acidosis, which may cause renal arteriolar vasoconstriction leading to oliguria and a slowing of the resolution of acidosis. Whilst using Hartmann's solution may avoid this problem, Hartmann's has other potential physiological disadvantages, although the clinical significance of these effects is debatable. The potential adverse effects of Hartmann's solution in the context of DKA include a lactate load that may increase the blood glucose and a potassium content that should be avoided in hyperkalaemic patients. Even though patients will often need more potassium than the $5mmol.L^{-1}$ potassium provided in Hartmann's

solution, the practice of adding potassium to Hartmann's is not licensed. Because 0.9% saline with either 20 or 40mmol.L$^{-1}$ potassium is readily available it has been recommended as a resuscitation fluid.

When the blood glucose reduces to 14mmol.L$^{-1}$ intravenous fluid should be changed to 10% glucose. This allows the insulin infusion to be continued, suppressing ketogenesis, while avoiding hypoglycaemia. 0.9% saline may need to be run simultaneously to correct any remaining circulatory volume deficit. Glucose should be continued until the patient is eating or drinking normally.

### Insulin therapy

A fixed rate intravenous insulin infusion (IVII) is recommended and is calculated as 0.1units.kg$^{-1}$.h$^{-1}$. A standard infusion mix is prepared by adding 50units actrapid insulin to 50mls 0.9% sodium chloride. If the patient normally takes a long acting insulin analogue (e.g. Lantus, Levemir), then this should be continued at their usual dose and time. It is no longer advised to administer a bolus dose of insulin at the time of diagnosis of DKA to allow rapid correction of blood sugar. Intravenous fluid resuscitation alone will reduce plasma glucose levels by two methods. It will dilute the blood glucose and also the levels of counter-regulatory hormones. Excessive insulin therapy causes inappropriately rapid falls in plasma glucose and risks profound hypokalaemia.

The aim is to reduce plasma blood glucose by 3mmol.L$^{-1}$ per hour. If the blood glucose falls too slowly, the insulin rate should be doubled every hour until the target decrease is met. If the blood glucose falls too quickly, the insulin rate can be halved to 0.05units.kg$^{-1}$.h$^{-1}$, but for a short time only, as a rate of 0.1 units.kg$^{-1}$.h$^{-1}$ is needed to switch off ketone production. If hypoglycaemia occurs prior to complete resolution of DKA, the insulin infusion should not be stopped, but extra glucose should be added to the IV fluids instead.

### Potassium replacement

In DKA there is a total body deficit of potassium. Despite this, at presentation mild to moderate hyperkalaemia is not uncommon. Serum levels will fall once insulin and fluids are started. Supplementary potassium is often required and may be provided by use of intravenous fluids containing between 20-40mmol.L$^{-1}$ KCl. Serum potassium should be maintained between 4.0-5.0mmol.L$^{-1}$. If the initial serum potassium is low (<3.3mmol.L$^{-1}$) then the insulin infusion should be withheld temporarily. Potassium is not routinely given in the first litre of 0.9% saline following resuscitation, unless more than 1L of saline was given in the early resuscitation stage. If the serum K$^+$ is above 5.3mmol.L$^{-1}$ potassium supplements should be omitted and serum potassium should be checked every 2 hours.

### Sodium bicarbonate

Sodium bicarbonate is rarely, if ever, necessary. If administered, potential deleterious effects include hypokalaemia, cerebral oedema and reduced tissue oxygenation, the latter by its effects on the oxygen dissociation curve. Acidosis will improve with fluid replacement and insulin. Continuing acidosis usually indicates insufficient resuscitation. Sodium bicarbonate should only be considered in patients with profound acidosis (pH< 6.9) and circulatory failure resistant to inotropes.

### Continuing management

#### Liaise with the Diabetic Specialist team

Involvement of the diabetic specialist team has been shown to shorten patient stay and improve safety.[1] The timing of their involvement will depend on local circumstances. They should be involved in the assessment of the precipitating cause of DKA, its ongoing management, discharge and follow up. They will also assess patients' knowledge and whether further diabetic education and lifestyle advice is warranted.

#### Location of care

Patients with DKA require close nursing and medical supervision. This may be best provided in a high dependency or intensive therapy environment if facilities are available. Arterial or central venous access may simplify management in patients with severe DKA by allowing regular monitoring of base excess, electrolytes and glucose in particular. Regular clinical assessment is mandatory so as to guide fluid therapy and ensure adequate resolution of shock.

#### Starting an insulin sliding scale and conversion to subcutaneous insulin

The fixed rate IVII should continued until blood ketones are below 0.3mmol.L$^{-1}$ and the blood pH is above 7.3. The insulin infusion should then be changed from a constant rate to a sliding scale. An example of a sliding scale is shown in Table 3. Oral diet should be resumed as soon as the patient is able. Subcutaneous insulin regimes may be commenced when the patient is tolerating an oral diet and is biochemically stable (ketones are below 0.3mmol.L$^{-1}$ and the blood pH is less than 7.3). Ideally give subcutaneous fast acting insulin and a meal and discontinue IV insulin one hour later.

#### Antibiotic therapy

Occult infections are common precipitants of DKA (Table 1). Evidence of infection should be actively sought and investigations should include blood cultures and urine dipstick testing and cultures.

**Table 3.** *Sliding scale for use in DKA once plasma glucose is less than 10mmol.L$^{-1}$.*

| Plasma glucose (mmol.L$^{-1}$) | Insulin (units.h$^{-1}$) | Additional action |
|---|---|---|
| <4 | 0.5 | Increase glucose intake. Repeat reading 30 minutes later |
| 4.0 - 6.0 | 1 | |
| 6.1 – 8.0 | 2 | |
| 8.1 – 10.0 | 4 | |
| 10.0 | 6 | Alert doctor if remains >10mmol.L$^{-1}$ after second reading |

Suspected bacterial infections should be treated aggressively with appropriate antibiotics. The role for prophylactic antibiotics in patients with DKA is an area of debate. The authors' preference is against this practice, but clinicians should consult local hospital guidelines.

*Thromboprophylaxis*

Patients with DKA are at increased risk of thromboembolism. Prophylactic heparin has an accepted role in the management of patients with DKA. It should be continued until patients are mobile, with no evidence of dehydration or elevated serum osmolality. Unfractionated heparin or low molecular weight heparin are both suitable treatments.

*Nasogastric tube drainage*

DKA causes gastric stasis. Aspiration pneumonitis may occur if vomiting is combined with a reduced level of consciousness. Nasogastric tube drainage should therefore be considered in all patients with DKA. It is mandatory in those with markedly impaired conscious level.

*Urinary catheterisation*

Strict fluid balance is required in the management of DKA. Measurement of urinary output is simplified by urinary catheterisation.

*Continuous ECG monitoring*

Where available, this is indicated in the presence of significant underlying cardiac disease, significant hyper- or hypokalaemia or severe DKA.

*Notes recording*

Adequate recording of regular clinical assessments and laboratory test results is vital. This process is made easier by the use of standard ward or high dependency care observation charts and serial results sheets for blood results. Specific DKA care pathway documents should be used if available.

## MANAGEMENT OF CHILDREN AND ADOLESCENTS IN DIABETIC KETOACIDOSIS

A full description of DKA management in children is beyond the scope of this edition. Although the pathophysiology behind DKA in children is the same as in adults, there are important differences, particularly concerning presentation and management.

For young people under the age of 18 years refer to the British Society of Paediatric Endocrinology and Diabetes (BSPED) guidelines: **http://www.bsped.org.uk/clinical/docs/ DKAGuideline.pdf**

*Major considerations for children with DKA*

- Smaller size mandates more precise prescription of fluids and electrolytes.

- Cerebral oedema is more common in children, occurring in up to 1%, with a mortality rate of up to 25%.[10] Less aggressive fluid replacement should be employed in children compared to adults.

- Fluid deficit is replaced over 48 hours and is calculated using the following equation:

Fluid requirement over 48 hours = Maintenance (over 48 hours) + deficit - fluid already given

where the deficit (in ml) = Body weight (kg) x % dehydration x 10

- Insulin should be avoided in the first hour of fluid replacement, sodium bicarbonate should be avoided altogether and the rate at which the blood glucose falls should be very carefully monitored and controlled.
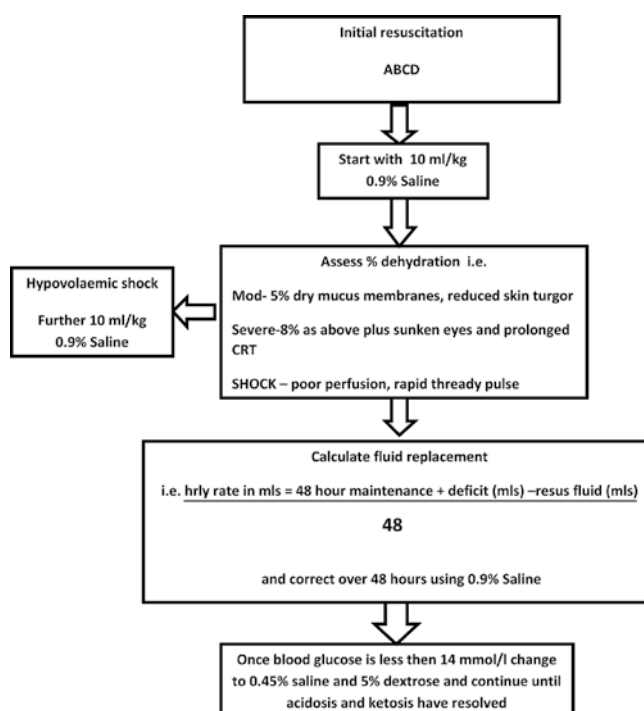


**Figure 1.** *Overview of management of DKA in children (Modified from: Glaser NS et al. Frequency of sub-clinical cerebral oedema in children with diabetic ketoacidosis. Pediatr Diabetes 2007; 8: 28-43).*

Remember overestimation of fluid loss is dangerous, therefore do not use more than 8% dehydration in calculations.

## COMPLICATIONS OF DKA TREATMENT

### Cerebral oedema

Monitoring for any signs of cerebral oedema should start at the time of admission of patients with DKA and continue for at least the first 12 hours of treatment. Cerebral oedema typically presents within 2 – 24 hours of treatment for DKA. Early signs are headache, confusion and irritability. Later signs include reduced conscious level and seizures.

As cerebral oedema usually occurs within a few hours of initiation of treatment, there has been speculation that it is iatrogenic. This has been disputed by some since sub-clinical cerebral oedema has been demonstrated before treatment has been started. Recent studies suggest that cerebral hypoperfusion with subsequent reperfusion may be the mechanism responsible.[1]

If cerebral oedema is suspected due to an altered level of consciousness, hypoglycaemia must be excluded initially. Intravenous mannitol (1.0g.kg$^{-1}$ = 5.0ml.kg$^{-1}$ 20% mannitol) should be given immediately. Fluids should be restricted to two-thirds maintenance and the fluid deficit should be replaced over 72 hours. Patients should be transferred to an Intensive Care Unit for intubation and mechanical ventilation and arrangements should be made for an urgent CT head. If cerebral oedema is present use of intracranial pressure monitoring should be discussed with a neurosurgeon.

### Hypoglycaemia

The blood glucose can fall very rapidly as ketoacidosis is corrected, and hypoglycaemia may ensue. This can lead to rebound ketosis, driven by counter-regulatory hormones, which has been shown to lengthen the duration of treatment. Severe hypoglycaemia is also associated with cardiac arrhythmias, acute brain injury and death. Hypoglycaemia should be treated with increased dextrose administration. A decreased insulin infusion rate may be necessary temporarily. Insulin infusions should not be stopped before the metabolic acidosis and ketonuria has resolved, as this will delay recovery.

### Hypokalaemia

Potassium levels should be monitored frequently by venous or arterial blood gas analysis, and hypokalaemia should be treated in a standard fashion. If potassium needs to be infused in a concentration of more than 40mmol.L$^{-1}$, then it must be given via a central line, with continuous cardiac monitoring.

### Hypophosphataemia

Hypophosphataemia is common. It seldom requires treatment as levels will correct once oral diet is resumed. The routine replacement of phosphate does not improve the outcome in DKA. However in those with cardiac dysfunction, anaemia or respiratory depression combined potassium and phosphate replacement can be given.

### DKA IN PREGNANCY

DKA in pregnancy is of special concern. It tends to occur at lower plasma glucose levels and more rapidly than in non-pregnant patients and usually occurs in the second and third trimesters because of increasing insulin resistance. Fetal mortality rates have previously been reported as high as 30%, rising to over 60% in comatose parturients with DKA.[11] However, with improvements in diabetic care, the figure for fetal loss has been reported to be as low as 9% in some countries.[12] Prevention, early recognition and aggressive management are vitally important to try to minimise fetal mortality. It is clear that diabetic and obstetric teams should jointly manage all pregnant patients with DKA. Additional support may be required from the critical care team.

### CONCLUSION

DKA is a potentially life threatening complication of diabetes mellitus. An understanding of the pathophysiology of the condition aids appropriate treatment. Initial assessment must involve a rapid assessment of Airway, Breathing, Circulation and Disability.

Immediate adequate intravenous access is required. Initial investigations are aimed at confirming the diagnosis and identifying underlying causes.

The basic principles of DKA management are:

- Rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids.

- Gradual rehydration and restoration of depleted electrolytes.

- Insulin to reverse ketosis and hyperglycaemia.

- Regular monitoring of clinical signs and laboratory tests to detect and treat complications.

- A target rate of correction of hyperglycaemia of 3 to 4mmol.L$^{-1}$.h$^{-1}$.

Acute cerebral oedema is a potentially fatal complication that is possibly caused by excessive fluid therapy or too rapid a fall in blood glucose. Early signs of the development of cerebral oedema include headache, irritation and confusion. Prompt recognition and appropriate management may improve prognosis.

### REFERENCES

1. Savage et al. Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults. March 2010.

2. Wittlesey CD. Case study: Diabetic ketoacidosis complications in type 2 Diabetes. *Clinical Diabetes* 2000; **18**: 88-90.

3. Faich GA, Fishbein HA, Ellis SE. The epidemiology of diabetic ketoacidosis: a population-based study. *Am J Epidemiol* 1983; **117**: 551-8.

4. Lin SF, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. *Chang Gung Med Journal* 2005; **28**: 24-30.

5. Hamblin PS, Topliss DJ, Chosich N et al. Deaths associated with diabetic ketoacidosis and hyperosmolar coma, 1973-1998. *Medical Journal of Australia* 1989; **151**: 439-44.

6. Kitabaci AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycaemic crises in adult patients with diabetes. A consensus statement from the American diabetes association. *Diabetes Care* 2006; **29**: 2739-48.

7. Dhatariya K. Editorial. Diabetic Ketoacidosis. *Brit Med J* 2007; **334**: 1284-5.

8. NPSA Patient Safety Alert 22. Reducing the risk of hyponatraemia when administering intravenous infusions to children. London 2007.

9. Patient Safety Alert. Potassium solutions: risk to patients from errors occurring during intravenous administration. London 2007.

10. Glaser NS et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes* 2007; **8**: 28-43.

11. Kyle GC. Diabetes and pregnancy. *Ann Intern Med* 1963; **59**: 1-8.

12. American Diabetes Association. Report on the expert committee on the diagnosis and classification of diabetes me mellitus. *Diabetes Care* 1999; **22** (Suppl 1): S5.