

The Management of Diabetic Ketoacidosis

MS Hammersley & JA Edge

Abstract

This article reviews the management of diabetic ketoacidosis (DKA) in adults with a focus on the three basic principles of treatment: intravenous fluid therapy, intravenous insulin administration and potassium replacement. The recommendations are modelled on the national guidance for the management of DKA in children.^{1,2} We highlight the importance of being alert to signs of life-threatening complications of the condition such as cerebral oedema and adult respiratory distress syndrome (ARDS). We also discuss the use of near-patient testing of capillary beta-hydroxybutyrate (β -OHB) using a ketone meter as an aid to managing and preventing DKA.

Keywords

DKA, Ketones, Betahydroxybutyrate (β -OHB), High dependency unit (HDU).

Keypoints

- Patients with DKA should ideally be managed in an HDU environment with early involvement of the diabetes specialist team.
- Fluid replacement should take place over 24–48 hours rather than over a 12 hour period.
- Insulin should be infused at a fixed rate (0.1 units/kg) until normalisation of pH.
- 'Stat' doses of insulin (im/iv/sc) at the initiation of treatment should be avoided.
- Hypokalaemia causes serious cardiac arrhythmias and muscle weakness (including diaphragmatic) and should be avoided by adequate potassium replacement throughout the treatment period.
- Measurement of capillary ketone levels aids therapy decisions.
- Hypoglycaemia is life-threatening and is preventable. Blood glucose (BG) should be kept between 8–11 mmol/L until the correction of metabolism is achieved.
- Glasgow coma scale (GCS) and oxygen saturation (O₂ sats) should be closely observed to detect life-threatening complications.

Introduction

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes caused by absolute or relative insulin deficiency. It commonly occurs in patients with type 1 diabetes (T1DM) but also occurs in some patients with type 2 diabetes (T2DM) who are often of Afro-Caribbean or

Hispanic origin; this is also known as ketosis-prone type 2 diabetes.³ The most common causes are discontinuation of insulin treatment, underlying infection, and new onset of diabetes. The mortality associated with DKA has remained at approximately 2–5%⁴ despite improved standards of care in the community.

Patients with DKA traditionally present to the medical admissions unit (MAU) or the emergency department (ED) and are, therefore, managed by non-specialist teams particularly in the first 24 hours. There is evidence that outcomes are better if these patients are managed by a specialist team.⁵ We strongly advise that the specialist diabetes team is involved at the earliest opportunity.

The case for the use of joint adult and paediatric guidelines

Those most likely to die from DKA are the elderly with important co-morbidities.⁴ However, young adults may be at risk of the rare complication of cerebral oedema. Certainly until the age of 15 years, the risk is around 5 per 1000 episodes of DKA,⁶ and anecdotal cases are known in young adults,⁷ but no studies have looked at the incidence of this complication in this age group. In children, predictors of cerebral oedema are low pH at presentation and severe dehydration.^{8–9} Excessive fluid resuscitation and early insulin treatment (within the first hour of commencement of fluids) are associated with an increased risk of cerebral oedema in children.⁸ In most hospitals in the UK, it is standard practice for children to 'graduate' to adult services when they are 16 years old, but it makes no physiological sense to change the DKA regimen dramatically at the 16th birthday.

Therefore, we recommend a change in practice in the administration of fluids and insulin in all adults and particularly in the 16–25 year old age group. We advise a more conservative approach to fluid replacement than has been previously advised.

- This guideline recommends 3 litres saline over 6 hours, whereas most protocols for DKA advise saline resuscitation of 3 litres in 3 hours.
- We no longer recommend a stat dose of insulin at the beginning of the treatment plan, to avoid

Dr MS Hammersley
Consultant Physician and
Acute Care Diabetologist
Senior Clinical Lecturer
Nuffield Department of
Medicine
John Radcliffe Hospital
Oxford OX3 9DU

Dr JA Edge
Consultant Paediatric
Endocrinologist
Department of Diabetes
and Endocrinology
Oxford Children's Hospital
Oxford OX3 9DU

Correspondence:
Dr MS Hammersley
Level 2 Secretariat
John Radcliffe Hospital
Oxford OX3 9DU
Email: maggie.hammersley@
orh.nhs.uk

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the sudden osmotic shift that may accompany a rapid fall in blood glucose.

- We advocate the use of a fixed dose IV insulin infusion, calculated on body weight (as recommended for use in children with DKA) and for this be continued until pH > 7.3 and there is clearance of ketones from the plasma.

Glucose > 11 mmol/L
pH < 7.3
HCO ₃ < 15 mmol/L
Presence of ketonaemia > 3 mmol/L
Presence of ketonuria

Table 1. Criteria for Diagnosis of DKA

Principles of treatment

A. General concepts

- All cases of suspected DKA referred to ED or acute medicine should be accepted and assessed by the physician on call.
- The diagnosis is made using the criteria in Table 1.
- Some patients present with ketosis without significant acidosis. Treatment with IV insulin in those with β -OHB levels > 3 mmol/L can prevent the onset of acidosis.
- Patients with DKA have severe metabolic derangement and require intensive bedside monitoring. Those with moderate or severe DKA should be managed in an HDU/ITU environment (see Table 2).

	pH	HCO ₃	Level of care
Mild	> 7.25	15–18	MAU or ward
Moderate	7.00–7.25	10–15	HDU
Severe	< 7.00	< 10	ITU

Table 2. Severity of DKA

B. Emergency Treatment

- **Airway.** A naso-gastric tube should be considered in a vomiting or semi-conscious patient.
- **Breathing** (monitor oxygen saturations).
- **Circulation and Contact senior help.** If severely fluid depleted, give 500 ml 0.9% saline over 15–20 minutes, otherwise commence 0.9% saline at 500ml/hr
- **Diagnosis** – baseline investigations to include urea, creatinine, venous glucose, venous blood gas analysis for pH, pO₂, pCO₂, HCO₃, base deficit, lactate, chloride and FBC and clotting. Anion gap should be calculated and recorded. An infection screen should include urine dipstick and culture and blood cultures and C-reactive protein level.
- If available, measure capillary ketone levels using Optium Xceed™ (measures up to a level of 8 mmol/L see below).
- Bicarbonate therapy is rarely, if ever, needed and decision to administer should be made by a suitably qualified consultant (see below)

C. Full clinical assessment and monitoring

The following parameters should be assessed and recorded.

- Degree of dehydration.
- Conscious level by documenting Glasgow Coma Scale (GCS) hourly and commence neurological observations if the patient is drowsy.
- Clinical examination is performed for evidence of infection or ARDS.
- Severity of DKA is assessed and appropriate action taken (see Table 2).
- Blood Glucose (BG) and β -OHB levels should be measured hourly.
- Check serum K⁺ and venous pH after 2 hours and at 4, 8, 12, 16 and 24 hours
- Fluid and insulin therapy changes should be made with reference to changes in ketone (or pH) level in addition to BG level.
- Check magnesium level at 12–24 hours.

A useful flow chart for the documentation of parameters measured during initial assessment and ongoing monitoring of patients with DKA can be downloaded from: http://www.diabetologists.org.uk/ABCD_DKA_chart.pdf

D. Management (see figure 1)

1. Fluid therapy

Fluid resuscitation is a critical part of treating DKA. Intravenous (IV) solutions replace intravascular and extravascular fluid and electrolyte losses. The administration of fluids also acts to dilute plasma glucose and to encourage the clearance and excretion of circulating counterregulatory hormones (catecholamines, glucagon, growth hormone and cortisol) which will increase tissue sensitivity to insulin.

Adults with DKA generally need an average of 6 litres' rehydration. The first priority is to expand the intravascular compartment. Colloid offers no benefit over crystalloid and is expensive.¹⁰ The choice of crystalloid is much debated. Most acute physicians and junior doctors are conversant with prescribing 0.9% saline and it is an appropriate, safe prescription of fluid in this condition and will result in expansion of all compartments. Adult intensivists tend to use Ringer's Lactate in an attempt to reduce the problem of the transient but inevitable rebound hyperchloraemic acidosis which occurs during treatment (see below). The differences between these fluid prescriptions are small and not clinically relevant. This guideline advises that 3 litres of saline be infused over 6 hours and a further 3 litres over 10 hours (Table 3).

FLUID	RATE
0.9% saline	500 ml/hr for first hour
0.9% saline with 40 mmol/L KCl	500ml/hr for 5 hrs
0.9% saline with 40 mmol/L KCl	300ml/hr for 10 hrs

Table 3. Recommended fluid resuscitation in DKA

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Fluid balance and ‘euglycaemic’ DKA.

Traditional protocols recommend a change from 0.9% saline to 5% dextrose when the plasma glucose reaches 15mmol/L but in ‘euglycaemic’ DKA (a clinical scenario where there is only trivial elevation of BG (e.g.12–25 mmol/L) in the presence of significant ketoacidosis, this can occur very early in the treatment period before correction of dehydration. Junior doctors following such protocols may be tempted to change to dextrose before the patients has received sufficient saline rehydration. It is important, in this instance, to ensure that a second infusion fluid which contains 5% or 10% dextrose is given to maintain the blood glucose between 8 and 11mmol/L, in order to prevent hypoglycaemia and provide sufficient substrate for the action of insulin until ketosis is switched off (Table 4).

This increasing trend for patients with DKA to present with only modest elevation in plasma glucose may be a result of patients self-administering additional subcutaneous insulin according to ‘sick day rules’ which result in minimal elevation in glucose despite significant acidosis.

Glucose monitoring	Fluids
If BM < 15 mmol/L in first 16 hours	Start 5% Dextrose with KCl infusion via 2nd line at rate of 125 ml/hr
If BM < 7mmol/L in first 16 hours	Change to 10% Dextrose with KCl at rate of 125 ml/hr

Table 4. Ensuring the provision of substrate in euglycaemic DKA

2. Insulin

Insulin is needed to help switch from a catabolic to an anabolic state which will result in an uptake of glucose into tissues and the reduction of gluconeogenesis. The end result of this is to switch off the production of free fatty acid and ketones.

- An infusion of insulin should be prepared by adding 50 units of human soluble insulin (Actrapid or Humulin S) to 50 ml of 0.9% saline.
- It is recommended that **insulin be infused at a constant rate of 0.1 units/kg per hour, until the correction of acidosis (pH > 7.3).**
- An average 20 year old male weighing 70 kg would require 7 units/hour.
- Aim for blood glucose (BG) to fall by 3–5 mmol/L per hour.
- If this does not occur in the first 2 hours the insulin rate should be increased by 1–2 units.
- The fall in plasma glucose will precede the fall in plasma ketones.
- It is anticipated that the ketone levels should fall by approximately 1 mmol/L per hour when the correct dose of insulin is infused.
- We recommend that this fixed rate of insulin is continued until there is clearance of ketones (< 0.3 mmol/L) and the pH is > 7.3 mmol/L
- If blood glucose falls to less than 15 mmol during this insulin infusion, then add dextrose to the fluids as shown in Table 4.

- If the patient is eating and drinking there should be a prompt transfer to subcutaneous insulin at this point. If, however, the patient remains clinically unwell, an intravenous insulin sliding scale should be commenced (Table 5).

Capillary glucose (BM) mmol/L	Insulin/hr
0–4.0	0.5 units
4.1–6.0	1 unit
6.1–8.0	2 units
8.1–10	3 units
> 10	4 units and consult with Dr to adjust sliding scale

Table 5. Example of an IV sliding scale appropriate for use in DKA when pH>7.3

3. Potassium

Hypokalemia and hyperkalemia are potentially life-threatening conditions during the management of DKA. There is a risk of acute pre-renal failure associated with severe dehydration and it is, therefore, recommended that no potassium be prescribed with the initial fluid resuscitation or if initial serum potassium level is > 5.5 mmol/L. Thereafter, it is recommended that 40 mmol KCl is added to each litre if K⁺ is < 5.5 mmol/L and the patient is passing urine. More may be required if K⁺ falls below 3.5 mmol/L (Table 6).

Potassium level	Potassium Replacement/litre fluid
> 5.5 mmol/L	Nil
3.5–5.5 mmol/L	40 mmol/L
< 3.5 mmol/L	60–80 mmol/L

Table 6. Recommended potassium replacement in DKA

E. Continuing management

a) Treatment of precipitant

If there is objective evidence of infection then this should be treated according to hospital guidelines. The white cell count is an unreliable indicator of infection as it is invariably raised in DKA. If insulin omission is the cause of DKA then it is essential to investigate the circumstances and refer to the specialist diabetes team. Recurrent admissions with DKA is often an indicator of emotional stress and poor coping and may need specialist psychological support.

b) Use of bicarbonate

The indications for bicarbonate therapy in DKA remain controversial. Several controlled trials of sodium bicarbonate in small numbers of children and adults have been unable to show clinical benefit, even at a pH as low as 6.8 and have in some cases actually shown slower resolution of acidosis.^{11–12} There are potential arguments against the use of bicarbonate. Firstly, bicarbonate therapy may cause paradoxical CNS acidosis and has been implicated in the development of cerebral oedema.⁷ Also rapid correction of acidosis caused by bicarbonate may result in profound hypokalaemia and may accentuate

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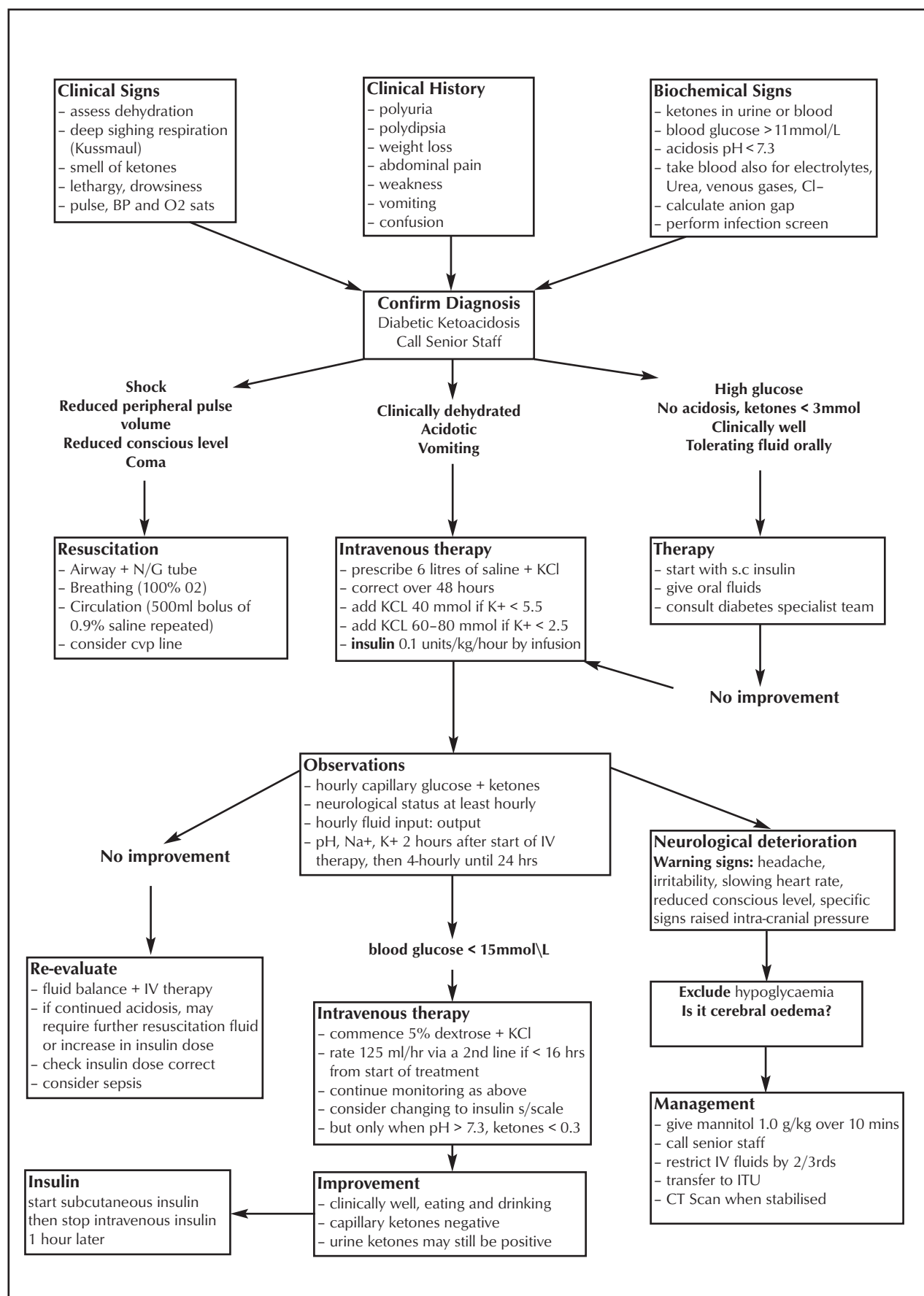


Figure 1. Algorithm for the Management of Diabetic Ketoacidosis

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sodium load and contribute to serum hypertonicity. Alkali therapy may independently increase hepatic ketone production and slow the rate of recovery from the ketosis. Bicarbonate should not, therefore, be used routinely when the presenting pH is > 6.8.

c) Phosphate and magnesium replacement

Phosphate levels are invariably low in patients with DKA. The replacement of phosphate does not improve outcomes and can lead to hypocalcaemia.¹³ It is, therefore, not routinely replaced. However, replacement of magnesium is advised at levels ≤0.7 mmol/L as most patients are symptomatic and there is a risk of cardiac arrhythmias.¹⁴

d) Thromboprophylaxis

Consider the use of low molecular weight heparin for prevention of venous thromboembolism, particularly in older patients with vascular co-morbidity.

e) Resolution of DKA

Therapy decisions have become easier with the advent of direct measurement of capillary β-OH butyrate rather than relying on surrogate indicators of disordered metabolism such as pH and HCO₃. The authors now routinely use the fall in ketone levels (usually 1 mmol/L per hour) as an indicator of appropriate insulin and fluid treatment in the management of DKA.¹⁵ It is safe to convert to a subcutaneous insulin regime when ketones are cleared from the plasma completely and the patient is eating and drinking, even if ketones (mostly acetoacetate) are still present in the urine. Where a ketone meter is not available we suggest that pH and HCO₃ should be used to define insulin adjustment not the plasma glucose. If patient is ketone-free, has a pH >7.3 but does not feel able to eat we advise a sliding scale of insulin (Table 5).

F. Complications

a) Cerebral oedema

Symptomatic cerebral oedema occurs primarily in children and young adults, particularly those with newly diagnosed diabetes. No single factor predictive for cerebral oedema has yet been identified. Cerebral oedema typically occurs 4–12 hours after treatment is activated, but can be present before treatment has begun, or may develop any time during treatment for DKA. Symptoms and signs of cerebral oedema are variable and include onset of headache, gradual decrease or deterioration in level of consciousness, inappropriate slowing of the pulse rate, and an increase in blood pressure. As noted previously, however, overly rapid rehydration appears to increase the risk of cerebral oedema, with falling plasma sodium levels being a marker.^{7,16} Onset of headache or mental status changes during therapy should lead to consideration of this complication. Intravenous mannitol in a dosage of 1–2 g per kg given over 15 minutes is the mainstay of therapy.²

b) Adult respiratory distress syndrome (ARDS)

This is an uncommon but potentially fatal complication of the treatment of DKA. Excessive crystalloid infusion favours the development of pulmonary oedema, even in the presence of normal cardiac function. Patients with an increased alveolar to arterial oxygen gradient (AaO₂) and patients with pulmonary crackles on physical examination may be at increased risk of ARDS.¹⁷ Monitoring of oxygen saturation with pulse oximetry may assist in the early detection of the condition. Once diagnosed these patients should be transferred to ITU as many will require ventilatory support.

c) Hyperchloraemic metabolic acidosis

A hyperchloraemic acidosis with a normal anion gap may persist even after the resolution of ketonaemia. This acidosis has no adverse clinical effects and is gradually corrected over the subsequent 24 to 48 hours by enhanced renal acid excretion.¹⁸

G. Prevention of DKA

The advent of a handheld ketone meter for home use has offered the opportunity for the prevention of DKA in patients with diagnosed diabetes. The Optium Xceed™ meter records capillary β-OHB level, which is the principle ketone produced in DKA. A recent consensus statement from the American Diabetes Association emphasised the importance of its use in current clinical practice.²⁰ Some glucose meters alert patients to test for ketones when the blood glucose is high, and a guideline for patient use is available to aid the interpretation of and to advise how to act upon a quantitative rise in ketone levels (Table 7).¹⁵

The uptake and use of ketone meters has been widely published in the paediatric literature²¹ with evidence of reduced admissions and health costs.²² Kitabchi speculates that increased use of the ketone meter in adults and better access to health care may help prevent adult DKA in the USA.²³ In clinical practice, the use of the ketone meter has been shown to prevent admissions with DKA in adult patients on continuous subcutaneous insulin infusion (CSII).²⁴ More recently, clinicians in the Emergency Department have published on its use to diagnose DKA promptly in adults and children.²⁵ There is also recent evidence that capillary ketone measurement has a useful place in the detection and management of DKA in other acute medical units in the UK.²⁶

β-OHB level	Action
0–1 mmol/L	No action
1–3 mmol/L	Increase sc insulin, ensure plenty of fluids and seek advice
> 3 mmol/L	Attend hospital – require iv insulin

Table 7. Guideline for patients in the use of the ketonemeter

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Conclusion

DKA is a serious complication that is common to both children and adults. Although the complications of DKA differ in incidence across the ages, there are still principles of management, which can cross the traditional boundaries. Excessive fluid administration may contribute to the ARDS seen in adults, just as it does to cerebral oedema in children, and should therefore be avoided in all. Insulin is necessary to switch off ketosis and should therefore be given at a constant rate with appropriate adjustments of the glucose content of the rehydration

fluid to prevent hypo and hyperglycaemia. Use of bedside ketone monitoring may help in prevention and in the acute management of DKA. Joint adult/child guidelines are possible and desirable.

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