

POSITION STATEMENT

The management of diabetic ketoacidosis in adults—An updated guideline from the Joint British Diabetes Society for Inpatient Care

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Funding information

None.

Abstract

This article summarises the Joint British Diabetes Societies for Inpatient Care guidelines on the management of ketoacidosis; available at <https://abcd.care/resource/management-diabetic-ketoacidosis-dka-adults>. The document explicitly states that when a person aged 16–18 is under the care of the paediatric team, then the paediatric guideline should be used, and if they are cared for by an adult team, then this guideline should be used. The guideline takes into account new evidence on the use of the previous version of this document, particularly the high prevalence of hypoglycaemia and hypokalaemia, and recommends that when the glucose concentration drops below 14 mmol/L, that de-escalating the insulin infusion rate from 0.1 to 0.05 units/kg/h should be considered. Furthermore, a section has been added to address the recognition that use of sodium glucose co-transporter 2 inhibitors is associated with an increased risk of euglycaemic ketoacidosis. The management of ketoacidosis in people with end-stage renal failure or on dialysis is also mentioned. Finally, the algorithms to illustrate the guideline have been updated.

KEYWORDS

diabetic ketoacidosis, guideline, management

1 | INTRODUCTION

Since it was first published in 2010, this guideline, and its update published in 2013, have been widely adopted or adapted across the United Kingdom and other parts of the world. It is often seen as the standard of care for the condition. Together with the guideline from the American Diabetes Association (ADA),¹ this remains one of the most frequently cited guidelines on the management of ketoacidosis. By 2018, the original version had been accessed, read or downloaded more than 100,000 times from

the ABCD and Diabetes UK websites. In addition the published concise version has remained in the top 10 most downloaded articles from the Diabetic Medicine website for many years. This document introduced a change from glucose-based management of the metabolic disorder to ketone based. Although controversial at the time, this has resulted in faster resolution of ketoacidosis and shorter length of stay in repeated audits.

When it was first written, while most of the advice was evidence based, some of the recommendations were consensus based. They were based on the collective

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experiences of the writing group. Since then, more evidence has become available to suggest not only that many of those recommendations were appropriate but also that a few may need to be amended.

This new edition aims to update the guidance using evidence that has become available. In other places, changes have been suggested based on expert consensus. These are highlighted in the controversial areas section.

Abbreviated versions of the guideline are shown in Figure 1, and also Figure 2 in the supplementary materials.

1.1 | Diagnosis of ketoacidosis

All of these must be present to make the diagnosis:

The 'D'—a blood glucose (BG) concentration of >11.0 mmol/L or known to have diabetes mellitus.

The 'K'—a capillary or blood ketone concentration of >3.0 mmol/L or significant ketonuria (2+ or more on standard urine sticks).

The 'A'—a bicarbonate concentration of <15.0 mmol/L and/or venous pH <7.3 .

The ADA definition is slightly different, and it also uses the anion gap as part of the diagnostic criteria to judge severity.¹ The most common equation to calculate anion gap is $([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$. There has been a call to update the ADA guideline.²

1.2 | Rationale for current practice

1.2.1 | Ketones and acidosis

With a greater understanding of acid–base chemistry and physiology, it is now well established that venous blood gas measurements alongside capillary ketone and glucose measurements are key to guiding the management of ketoacidosis.

Data from a national survey carried out in 2014 in the United Kingdom showed that 76% of institutions had the ability to measure ketone concentrations using point-of-care testing.³ The 2020 report of the 2019 National Inpatient Diabetes Audit (NaDIA) showed that 71.3% of hospitals used remote (networked) glucose meters.⁴ Diabetes UK also recommended the use of remote glucose and ketone monitors in their 2018 report entitled 'Making Hospitals Safe for People with Diabetes'.⁵

1.2.2 | Euglycaemic ketoacidosis

This is the development of raised anion gap metabolic acidosis, ketonaemia (>3.0 mmol/L) or significant ketonuria

What's new?

- Ketoacidosis remains a potentially life-threatening condition. The previous version of this guideline has been used extensively across the United Kingdom and elsewhere. However, evidence on the prevalence of hypoglycaemia and hypokalaemia suggested that changes were needed.
- This guideline explicitly states that when a person aged 16–18 years old is under the care of the paediatric team, then the paediatric guideline should be used, and if they are cared for by an adult team, then this guideline should be used.
- This updated guideline now recommends considering de-escalating the insulin infusion rate from 0.1 to 0.05 units/kg/h once the blood glucose falls below 14 mmol/L.
- New sections have been added to address the issue of euglycaemic ketoacidosis with the use of SGLT-2 inhibitors, ketosis prone type 2 diabetes and ketoacidosis in those with end-stage renal failure or on dialysis.

(2+ or more on standard urine sticks) in people known to have diabetes but where the glucose is normal, or not particularly raised. Improved education for those with diabetes with increased home capillary glucose and ketone monitoring has led to partial treatment of ketoacidosis prior to admission with consequent lower BG levels at presentation. This condition is treated in exactly the same way as hyperglycaemic ketoacidosis.

1. Initiate glucose 10% straight away at 125 ml/h because the glucose is <14 mmol/L
2. Begin with 0.1 units/kg/h insulin rate
3. If glucose falling despite 10% glucose reduce to 0.05 units/kg/h to avoid hypoglycaemia

With the widespread use of the sodium-glucose cotransporter (SGLT) inhibitor class of drugs (e.g., dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, sotagliflozin) in people with type 2 diabetes, and increasingly in those with type 1, has highlighted the importance of using pH and ketones (rather than the older 'glucose-centric' care) to guide the diagnosis and management. This is because of the risk of developing euglycaemic ketoacidosis with these agents.⁶ The rates of euglycaemic ketoacidosis prior to the widespread use of SGLT inhibitors showed that it was not uncommon.⁷ However, the rates of SGLT-associated ketoacidosis in the 'real world',



The Management of Diabetic Ketoacidosis in Adults



Where individuals aged 16-18 are managed by paediatric teams, the paediatric guidelines should be followed:

<https://www.bsped.org.uk/media/1943/bsped-guideline-for-the-management-of-children-and-young-people-under-the-age-of-18-years-with-diabetic-ketoacidosis-2021.pdf>

Diagnostic criteria: **all three of the following must be present**

- capillary blood glucose above 11 mmol/L
- capillary ketones above or equal to 3 mmol/L or urine ketones ++ or more
- venous pH less than 7.3 and/or bicarbonate less than or equal to 15 mmol/L

BOX 1: Immediate management: time 0 to 60 minutes

(T=0 at time intravenous fluids are commenced)

If intravenous access cannot be obtained request critical care support immediately

- Action 1:** Commence 0.9% sodium chloride solution (use a large bore cannula) via an infusion pump
See Box 2 for rate of fluid replacement
- Action 2:** Commence a fixed rate intravenous insulin infusion (FRII), (0.1 unit/kg/hr based on estimate of weight) 50 units human soluble insulin (Actrapid® or Humulin S®) made up to 50 ml with 0.9% sodium chloride solution. If patient normally takes long acting insulin analogue (glargine, detemir, degludec) continue at usual dose and time
- Action 3:** Assess patient
 - Respiratory rate; temperature; blood pressure; pulse; oxygen saturation
 - Glasgow Coma Scale
 - Full clinical examination
- Action 4:** Further investigations
 - Capillary and laboratory glucose
 - Venous BG
 - U&E and FBC
 - Blood cultures
 - ECG
 - CXR
 - MSU
- Action 5:** Establish monitoring regimen
 - Hourly capillary blood glucose
 - Hourly capillary ketone measurement if available
 - Venous bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter
 - 4 hourly serum electrolytes
 - Continuous cardiac monitoring if required
 - Continuous pulse oximetry if required
- Action 6:** Identify and manage precipitating cause

HDU/level 2 facility and/or insertion of central line may be required in following circumstances (request urgent senior review)

- Young people aged 18-25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities
- Severe DKA by following criteria
 - Blood ketones above 6 mmol/L
 - Venous bicarbonate below 5 mmol/L
 - Venous pH below 7.1
 - Hypokalaemia on admission (below 3.5 mmol/L)
 - GCS less than 12
 - Oxygen saturation below 92% on air (Arterial blood gases required)
 - Systolic BP below 90 mmHg
 - Pulse over 100 or below 60 bpm
 - Anion gap above 16 [Anion Gap = (Na⁺ + K⁺) - (Cl⁻ + HCO₃⁻)]

BOX 2: Initial fluid replacement

Restoration of circulating volume is priority

Systolic BP (SBP) below 90 mmHg

Likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.

- Give 500 ml 0.9% sodium chloride solution over 10-15 minutes. If SBP remains <90 mmHg repeat whilst awaiting senior input. Most people require between 500-1000 ml given rapidly
- Involve the ITU / critical care team if the SBP remains <90 mmHg after 2 IV fluid boluses

Once SBP is >90 mmHg, give 1 L 0.9% sodium chloride over the next 60 minutes. The addition of potassium is likely to be required in this second litre of fluid

Systolic BP on admission 90 mmHg and over

Give 1 L 0.9% sodium chloride over the first 60 minutes

Potassium replacement Potassium level (mmol/L)	Potassium replacement mmol/L of infusion solution
>5.5	Nil
3.5-5.5	40 mmol/L
<3.5	senior review – additional potassium required

BOX 3: 60 minutes to 6 hours

Aims of treatment:

- Rate of fall of ketones of at least 0.5 mmol/L/hr OR bicarbonate rise 3 mmol/L/hr and blood glucose fall 3 mmol/L/hr
- Maintain serum potassium in normal range
- Avoid hypoglycaemia

Action 1: Re-assess patient, monitor vital signs

- Hourly blood glucose (lab blood glucose if meter reading 'HI')
- Hourly blood ketones if meter available
- Venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter
- If potassium is outside normal range, re-assess potassium replacement and check hourly. If abnormal after further hour seek immediate senior medical advice.

Action 2: Continue fluid replacement via infusion pump as follows:

- 0.9% sodium chloride 1 L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1 L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1 L with potassium chloride over next 4 hours
- Add 10% dextrose 125 ml/hr if blood glucose falls below 14 mmol/L
- Consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr when glucose falls below 14 mmol/L

More cautious fluid replacement in people aged 18-25 years, elderly, pregnant, heart or renal failure. (Consider HDU admission)

Action 3: Assess response to treatment

- Insulin infusion rate may need review if
 - Capillary ketones not falling by at least 0.5 mmol/L/hr
 - Venous bicarbonate not rising by at least 3 mmol/L/hr
 - Plasma glucose not falling by at least 3 mmol/L/hr
 - Continue FRII until ketones less than 0.3 mmol/L, venous pH >7.3 and/or venous bicarbonate over 18 mmol/L

If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction).

If equipment working but response to treatment is inadequate, increase insulin infusion rate by 1 unit/hr increments hourly until targets achieved.

Additional measures

- Regular observations and Early Warning Score (NEWS2)
- Accurate fluid balance chart, minimum urine output 0.5 ml/kg/hr
- Consider urinary catheterisation if incontinent or anuric (not passed urine) by 60 minutes
- Nasogastric tube with airway protection if patient obtunded or persistently vomiting
- Measure arterial blood gases and repeat chest radiograph if oxygen saturation less than 92%
- Thromboprophylaxis with low molecular weight heparin
- Consider ECG monitoring if potassium abnormal or concerns about cardiac status

BOX 4: 6 to 12 hours

Aims:

- Ensure clinical and biochemical parameters improving
- Continue IV fluid replacement
- Avoid hypoglycaemia
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Treat precipitating factors as necessary

Action 1: Re-assess patient, monitor vital signs

- If patient not improving by criteria in Box 3, seek senior advice
- Continue IV fluid via infusion pump at reduced rate
 - 0.9% sodium chloride 1 L with KCl over 4 hours
 - 0.9% sodium chloride with KCl over 6 hours
 - Add 10% dextrose 125 ml/hr if the glucose falls below 14 mmol/L
- Consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr when glucose falls below 14 mmol/L

Reassess cardiovascular status at 12 hours; further fluid may be required

Check for fluid overload

Action 2 – Review biochemical and metabolic parameters

- At 6 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution of DKA is defined at ketones <0.3 mmol/L AND venous pH >7.3 (do not use bicarbonate as a marker at this stage)
- Ensure a referral has been made to the diabetes team
- If DKA not resolved review insulin infusion (see BOX 3 Action 3)
- If DKA resolved go to BOX 6

BOX 5: 12 to 24 HOURS

Expectation: By 24 hours the ketonaemia and acidosis should have resolved. Request senior review if not improving

Aim:

- Ensure that clinical and biochemical parameters are continuing to improve or are normal
- Continue IV fluid replacement if not eating and drinking
- If ketonaemia has cleared and the person is not eating or drinking, move to a variable rate intravenous insulin infusion (VRII) as per local guidelines
- Reassess for complications of treatment, e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors
- Transfer to subcutaneous insulin if the person is eating and drinking normally and biochemistry is normal

Action 1 – Re-assess patient, monitor vital signs

Action 2 – Review biochemical and metabolic parameters

- At 12 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones <0.3 mmol/L, venous pH >7.3
- If not resolved review fluid Box 4 Action 1 and insulin infusion Box 3 Action 3

Action 3

If DKA resolved go to Box 6

BOX 6: Resolution of DKA

Expectation: Patient should be eating and drinking and back on normal insulin

If DKA not resolved identify and treat the reasons for failure to respond. This situation is unusual and requires senior and specialist input

Transfer to subcutaneous insulin

Convert to subcutaneous regime when biochemical stable (capillary ketones less than 0.3 mmol/L AND pH over 7.3) and the patient is ready and able to eat. Do not discontinue intravenous insulin until 30 minutes after subcutaneous short acting insulin has been given. Conversion to subcutaneous insulin should be managed by the Specialist Diabetes Team. If the team is not available use local guidelines. If the patient is newly diagnosed it is essential they are seen by a member of the specialist team prior to discharge. Arrange follow up with specialist team

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WEDS
The Association for Clinical Biochemistry & Laboratory Medicine

DISN
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Represented: Association of British Clinical Diabetologists; British Society for Endocrinology and Diabetes and Association of Children's Diabetes Clinicians; Diabetes Inpatient Specialist Nurse (DISN) Group; Diabetes UK; Diabetes Network Northern Ireland; Society of Acute Medicine; Welsh Endocrine and Diabetes Society; Scottish Diabetes Group.

FIGURE 1 Pathway for the management of ketoacidosis

that is, outside of the trial population are not yet known, but may be higher than the trial data suggest. This is because of the careful selection, education and follow-up of trial participants as well as the differing definitions of ketoacidosis used in the trials.^{8,9}

If ketoacidosis occurs with SGLT inhibitor use, they should be stopped. The regulatory authorities should be made aware of an adverse drug reaction. In the United Kingdom, this is via the 'Yellow Card' system. Whether the drugs should be restarted once the individual has recovered should be discussed with the diabetes team.

1.2.3 Ketosis-prone type 2 diabetes

Ketoacidosis does not exclusively occur in people with type 1 diabetes, and people with type 2 diabetes may also develop ketoacidosis—the so-called 'ketosis-prone type 2 diabetes'.¹⁰ This most often occurs in people of Afro-Caribbean or Hispanic descent. The treatment for this condition is the same as for others with ketoacidosis, but they often come off insulin quickly after the

resolution of the ketoacidosis and underlying precipitating condition.

1.2.4 Differential diagnosis

It is important to exclude other cause of ketoacidosis, such as alcoholic ketoacidosis and starvation ketosis.

In alcoholic ketoacidosis, the normal glucose concentration is the key difference with ketoacidosis—however, a careful history needs to be taken to differentiate it from euglycaemic ketoacidosis. Ketoacidosis without a raised glucose in a person with alcoholism is virtually diagnostic of alcoholic ketoacidosis.¹¹ If alcoholic ketoacidosis is suspected, then capillary β-hydroxybutyrate should be measured and not urine ketones because acetoacetate production can be suppressed in alcoholic ketoacidosis. In addition, acetoacetate is measured by urinary dipstick.

Starvation ketosis occurs due to a lack of carbohydrate intake and usually develops over several days. The low carbohydrate intake will lead to low insulin secretion, subsequent

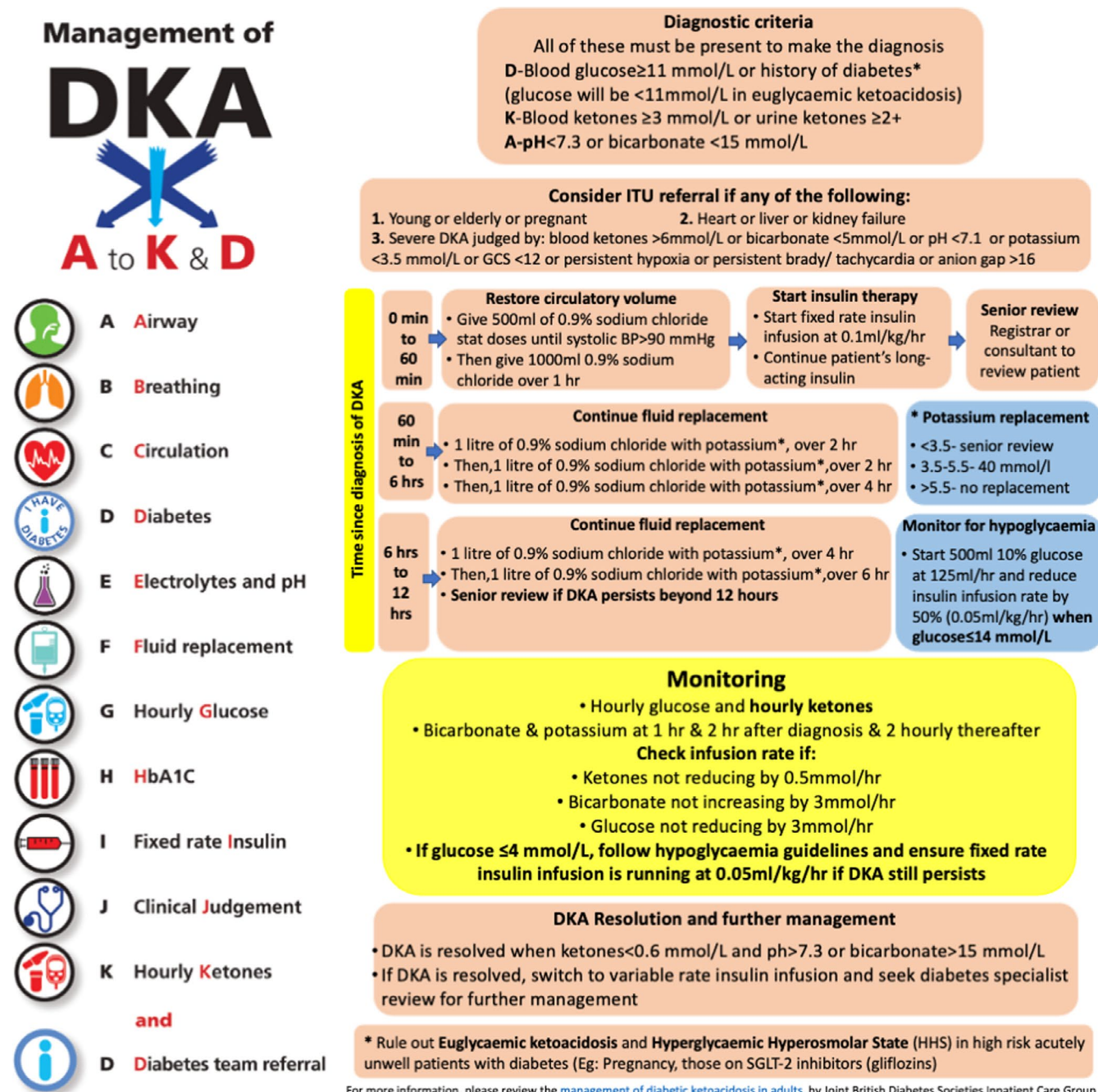


FIGURE 2 An example of a simplified pathway for the management of ketoacidosis—reproduced by Kind Permission of Punith Kempegowda

lipolysis and ketosis. Ketone concentrations can rise to over 6 mmol/L.¹² However, because this condition arises over a prolonged period, renal compensation for the acidosis means that (as long as other nutrients are eaten) acid-base and electrolyte disturbances are often minimal.¹³

1.2.5 | Point-of-care testing ('bedside monitoring')

These guidelines recommend that management be based on point-of-care testing of those admitted with

ketoacidosis. BG is routinely checked using point-of-care testing, but portable ketone meters now also allow point-of-care testing of 3-beta-hydroxybutyrate, the main blood ketone. Blood ketone measurement represents best practice in monitoring the response to treatment.¹⁴ There have been some concerns raised about their accuracy,¹⁵ but, to date, no harm has been reported from their use, and the data from these meters are just one of the measurements that helps to guide therapy and diagnose resolution.

Access to blood gas and blood electrolyte measurement is now relatively easy and available within a few minutes

of blood being taken. Venous blood gas can be used safely.^{16–18} Therefore, glucose, ketones and electrolytes, including bicarbonate and venous pH, should be assessed at or near the bedside using point-of-care testing.

The data informing these recommendations raise important issues³:

- Staff must be trained in the use of point-of-care BG and ketone meters in line with local point-of-care testing policy and demonstrate continuing competence in their use
- The meters should be subject to rigorous quality assurance
- Laboratory measurement will be required in certain circumstances, such as when BG or ketone meters are 'out of range'
- Staff should be made aware of the interferences affecting glucose meters and of the pre-analytical effects such as peripheral shutdown and shock

Furthermore, initial training with regular updates and/or revalidation should be implemented for all health care staff using POCT equipment and managed in line with local laboratory guidance. Additionally, point-of-care testing meters must be regularly checked with internal quality control material and a subscription to an external quality assessment scheme must be undertaken to ensure correct functionality of the meters.

It is recognised that almost all units now have access to ketone meters. However, guidance is also given on monitoring treatment using the rate of rise of bicarbonate and fall in BG as alternative measures.

2 | THE INVOLVEMENT OF DIABETES SPECIALIST TEAMS

The diabetes specialist team must always be involved in the care of those admitted to hospital with ketoacidosis. Their involvement shortens hospital stay and improves safety^{19,20}. This should occur as soon as possible during the acute phase but will depend on local circumstances. In line with the Best Practice Tariff for ketoacidosis, specialists must also be involved in the assessment of the precipitating cause of ketoacidosis, management, discharge and follow-up^{21,22}. This should include assessment of the understanding of the condition by person with diabetes (PWD) plus their attitudes and beliefs as well as ensuring the provision of structured education. Specialist involvement is essential to ensure regular audit and continuous quality improvement in the implementation of ketoacidosis guidelines. The practice of admitting, treating and discharging those with

ketoacidosis without the involvement of the diabetes specialist team is likely to compromise safe patient care. Regular auditing and monitoring of ketoacidosis outcomes and performance of specialist and non-specialist teams may not be routinely done.³

2.1 | General management issues

2.1.1 | Fluid administration and deficits

There is universal agreement that the most important initial therapeutic intervention in ketoacidosis is appropriate fluid replacement followed by insulin administration.

The main aims for fluid replacement are as follows:

- Restoration of circulatory volume
- Clearance of ketones
- Correction of electrolyte imbalance

The typical fluid and electrolyte deficits are shown in the Table 1. For example, an adult weighing 70 kg presenting with ketoacidosis may be up to 7 L in deficit. This should be replaced as crystalloid. In people with kidney failure or heart failure, as well as the elderly and adolescents, the rate and volume of fluid replacement may need to be modified. The aim of the first few litres of fluid is to correct any hypotension, replenish the intravascular deficit and counteract the effects of the osmotic diuresis with correction of the electrolyte disturbance.

The initial fluid replacement of choice is 0.9% sodium chloride solution. But once the BG falls below 14.0 mmol/L, a 10% dextrose infusion should be added to act as the substrate for the insulin, to prevent hypoglycaemia. Why these types of fluids are used is discussed in detail in *Controversial Areas*.

2.1.2 | Insulin therapy

A fixed-rate intravenous insulin infusion (FRIII) calculated on 0.1 units/per kilogram body weight is recommended (see Table 2). It may be necessary to estimate the weight of the individual. Insulin has several effects,

TABLE 1 Typical deficits in ketoacidosis in adults

Water	100 ml/kg
Sodium	7–10 mmol/kg
Chloride	3–5 mmol/kg
Potassium	3–5 mmol/kg

TABLE 2 Calculation of the insulin dose for weight

Weight in kg	Insulin dose per hour (units) at 0.1 units/kg/h if glucose ≥ 14 mmol/L
40–49	4
50–59	5
60–69	6
70–79	7
80–89	8
90–99	9
100–109	10
110–119	11
120–130	12
130–139	13
140–150	14
>150	15 (any dose higher than this should be on the advice of the Diabetes Specialist Team)
Weight in kg	Insulin dose per hour (units) at 0.05 units/kg/hour if glucose <14 mmol/L
40–49	2
50–59	2.5
60–69	3
70–79	3.5
80–89	4
90–99	4.5
100–109	5
110–119	5.5
120–130	6
130–139	6.5
140–150	7
>150	7.5

but the following are the most important when treating ketoacidosis:

- Suppression of ketogenesis
- Reduction of BG
- Correction of electrolyte disturbance

The insulin infusion is made up of 50 units of soluble human insulin in 49.5 ml 0.9% sodium chloride solution (i.e., 1 unit/ml). A Table 2 assist in the calculation of the insulin dose for weight:

Once the glucose drops to <14 mmol/L then in addition to adding a 10% dextrose infusion consider reducing the rate of intravenous insulin infusion to 0.05 units/

kg/h to avoid the risk of developing hypoglycaemia and hypokalaemia.

2.1.3 | Metabolic treatment targets

The recommended targets are

- Reduction of the blood ketone concentration by 0.5 mmol/L/h
- Increase the venous bicarbonate by 3.0 mmol/L/h
- Reduce capillary BG by 3.0 mmol/L/h
- Maintain potassium between 4.0 and 5.5 mmol/L

If these targets are not achieved, then the FRIII rate should be increased (see Management of DKA Section B, Action 2).

2.1.4 | Continuation of basal and intravenous insulin and intravenous glucose concentration

To ensure that ketones are cleared, an FRIII should be continued as well as an infusion of 0.9% sodium chloride solution to maintain fluid replacement. But once the BG falls below 14.0 mmol/L, a 10% dextrose infusion should be added to act as the substrate for the insulin, to prevent hypoglycaemia. It is quite often necessary to infuse 0.9% sodium chloride solution and 10% dextrose concurrently (Section B, Action 2). The intravenous insulin and dextrose should not be discontinued until the PWD is eating and drinking normally.

In those already on long-acting basal insulin, it should continue to be prescribed at their usual dose. In those newly diagnosed, then a long-acting basal insulin should be commenced, at a dose of 0.25 units/Kg subcutaneously once daily.

2.2 | Special groups

The following groups need specialist input as soon as possible and special attention needs to be paid to their fluid balance:

- Elderly
- Pregnant
- Young people 18–25 years of age (see section on cerebral oedema)
- Heart or kidney failure
- Other serious co-morbidities

2.3 | Other considerations

In line with several aspects of the Best Practice Tariff, people with diabetes who are admitted with ketoacidosis should be referred to the diabetes specialist team within one working day. Every opportunity should be taken to educate the PWD. In particular, they should be counselled about the precipitating causes and early warning symptoms. Things to consider are:

- Identification of precipitating factor(s), for example, intercurrent illness or omission of insulin injections
- Review of their usual glycaemic control
- Review of their injection technique/BG monitoring/equipment/injection sites
- For those on insulin pumps, review of their use of the device and provision of further education in the use of such technology, as necessary
- Prevention of recurrence, for example, provision of written sick day rules
- Insulin effectiveness, for example, their own insulin may be expired or denatured. This should be checked prior to reuse
- Assess the need for, and where necessary, provision of handheld ketone meters for use at home—this should be the default position
- Provision of a contact number on how to contact the diabetes specialist team out of hours
- Education of health care professionals on the management of ketonaemia
- Provision of a written care plan—allowing the PWD to have an active role in their own diabetes management, with a copy of this going to their GP
- For those with recurrent admissions, there is often a psychological element (e.g., eating disorders, other undiagnosed mental health disorders), that is likely to benefit from formal mental health team involvement

2.4 | Recurrent ketoacidosis

People who present with recurrent episodes of ketoacidosis (i.e., more than one episode per year) comprise a significant proportion of all ketoacidosis admissions—in the United Kingdom accounting for 66% of those with type 1 diabetes and 35% of those with type 2 diabetes.²³ Many of these individuals have fragmented care, social, behavioural or psychological considerations that need to be accounted for.^{24,25} Other risk factors for recurrent episodes include female sex, adolescence, low socio-economic status and previous ketoacidosis admissions. Recurrent episodes of ketoacidosis are associated with increased risk of long-term cognitive decline and premature mortality.^{26,27}

Strategies to help individuals may include frequent telephone contacts, formal referral to psychology, supervised insulin administration—for example, using ultra-long-acting insulin analogues.

2.5 | Controversial areas

Although the clinical assessment and aims of treatment in the management of ketoacidosis are not controversial, there is still disagreement about the optimum treatment regimen. Where the evidence base is not strong, recommendations are based on consensus and experience. Some of the more controversial points will now be considered and good practice recommendations are made. The recommendations are given first followed by the rationale. Differences between the United States and United Kingdom guidelines are discussed elsewhere.²⁸

There were a number of issues that were considered 'controversial' in the previous versions of this document, which have now become standard practice. These have been removed from this section. These are as follows:

1. Measure venous rather than arterial bicarbonate and pH
2. Blood ketone meters should be used for point-of-care testing
3. 0.9% sodium chloride solution is the recommended fluid of choice on the general medical ward (recommended as it is commercially available with premixed potassium chloride, and therefore, complies with NPSA recommendation)
4. Subcutaneous long-acting analogue/human insulin should be continued
5. Insulin should be administered as an FRIII calculated on body weight
6. Do not use a priming (bolus) dose of insulin

2.6 | Recommendations

1. Consider reducing the rate of insulin infusion to 0.05 units/kg/h when glucose drops to <14 mmol/L
2. Crystalloid rather than colloid solutions are recommended for fluid resuscitation
3. 0.9% sodium chloride solution ('normal saline') is the fluid resuscitation of choice
4. Cautious fluid replacement in young adults
5. Bicarbonate administration is not recommended routinely
6. Phosphate should not be supplemented routinely
7. The rate of glucose lowering should be least 3.0 mmol/L/h

1. Consider reducing the rate of insulin infusion to 0.05 units/kg/h when glucose drops to <14.0 mmol/L

A national survey of ketoacidosis management following earlier version of this guideline found that the rates of hypoglycaemia (<4.0 mmol/L) and hypokalaemia (<4.0 mmol/L) were 27.6% and 67% respectively. Although it may have been that these occurred due to 10% dextrose not being added in a timely manner, or that potassium containing fluids were not given correctly, the main driver for both of these biochemical abnormalities is the use of insulin. Thus, when glucose drops below 14 mmol/L, consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr. This is already an option in the adult guidelines elsewhere,²⁴ and several paediatric studies have suggested that the rate of resolution of ketoacidosis is not longer compared with 0.1 units/kg/h.^{29–31} It is, thus, also included in the United Kingdom paediatric guidelines.³²

2. Colloid versus crystalloid?

A 2007 Cochrane review also did not support the use of colloid in preference to crystalloid fluid.³³ A further 2013 consensus document suggested that colloids should be avoided where possible, due to a potential risk of increased mortality and morbidity associated with their use.³⁴ Therefore, we recommend the use of crystalloid fluid as the initial fluid of choice.

3. 0.9% sodium chloride solution or balanced crystalloid solution for resuscitation?

There has been much debate about the relative merits of these two solutions.³⁵ Two randomised trials have compared 0.9% sodium chloride solution with Hartmann's solution.^{36,37} Neither has shown the superiority of one fluid over the other in terms of clinical outcomes. More recently, a post hoc secondary subgroup analysis of two trials conducted in the emergency room suggested that balanced crystalloid may lead to faster resolution of ketoacidosis than 0.9% sodium chloride.³⁸ This limits crystalloid

use to environments where central venous access is available, and higher potassium concentrations may be given.³⁸

The result of a systematic review on the choice of crystalloid fluid replacement in hyperglycaemic emergencies is awaited.³⁹ Until then, we continue to recommend that 0.9% sodium chloride with pre-mixed potassium chloride be the default solution for fluid resuscitation because it is compliant with NPSA recommendations. Furthermore, diabetes specialists and physicians have a vast experience in the safe use of this fluid. We also recognise that many critical care units will prefer to use balanced crystalloids such as Hartmann's solution. This is acceptable provided local policies are followed for the safe administration of additional potassium chloride (Table 3).

4. Rate of fluid replacement?

For many years, there has been concern that rapid fluid replacement may lead to cerebral oedema in children and young adults. Until 2018, no randomised controlled trials existed to guide decision making in this area. However, a large, randomised controlled trial of 1389 episodes of ketoacidosis randomised children between 0 and 18 years of age to either 0.45% or 0.9% sodium chloride solution given fast or slow (i.e., a 2 by 2 factorial trial).⁴⁰ Reassuringly, these authors found no differences in neurological outcomes in children with ketoacidosis treated with rapid versus slower volume correction or with the use of 0.9% versus 0.45% sodium chloride. It is felt that the development of cerebral oedema is multifactorial, but often idiosyncratic.⁴¹

5. Intravenous bicarbonate?

Adequate fluid and insulin therapy will resolve the acidosis in DKA, and the use of bicarbonate is not indicated.^{42–45} The acidosis may be an adaptive response as it improves oxygen delivery to the tissues by causing a right shift of the oxygen dissociation curve. Excessive bicarbonate may cause a rise in the CO₂ partial pressure

TABLE 3 Advantages and disadvantages of infusion solution

Infusion solution	Advantages	Disadvantages
0.9% sodium chloride	<ul style="list-style-type: none"> Decades of clinical experience Readily available in clinical areas Commercially available ready mixed with potassium at required concentrations, 20 mmol/L (0.15%) or 40 mmol/L (0.3%) Supports safe practice with injectable potassium (NPSA compliant (NPSA alert 2002)) 	<ul style="list-style-type: none"> Hyperchloraemic metabolic acidosis, which may cause renal arteriolar vasoconstriction leading to oliguria and a slowing of resolution of acidosis
Compound sodium lactate (Hartmann's) solution	<ul style="list-style-type: none"> Balanced crystalloid with minimal tendency to hyperchloraemic metabolic acidosis 	<ul style="list-style-type: none"> Insufficient potassium if used alone Not commercially available with adequate pre-mixed potassium. Potassium addition in general clinical areas is unsafe. (NPSA alert 2002) Unfamiliar and not routinely kept on medical wards

in the cerebrospinal fluid (CSF) and may lead to a paradoxical increase in CSF acidosis.⁴² In addition, the use of bicarbonate in ketoacidosis may delay the fall in blood lactate:pyruvate ratio and ketones compared with intravenous 0.9% sodium chloride infusion.⁴³ Intensive care teams may occasionally use intravenous bicarbonate if the pH remains low and inotropes are required.

6. Use of intravenous phosphate?

Phosphate concentrations are often done as standard when a 'bone profile' is requested. Despite initial serum concentrations appearing normal, significant intracellular depletion means that whole-body phosphate deficits in ketoacidosis are substantial, averaging 1 mmol/kg of body weight. Severe phosphate deficiency can worsen respiratory failure, precipitate cardiac arrhythmias and cause rhabdomyolysis. If any of these are present phosphate measurement and replacement should be considered as per local guidance.^{24,46} In general, however, there is no evidence of benefit of routine phosphate replacement.⁴⁷ Therefore, we do not recommend the routine replacement of phosphate.

7. What should the rate of glucose lowering be?

The data from the studies published in the 1970s^{48,49} showed that using low-dose insulin infusions (i.e., 0.1 units/kg/h) resulted in glucose levels coming down at about the same rate as the high-dose insulin given in the preceding decades, with glucose levels coming down by about 50%–60% in the first 4 h. The theoretical risk of large osmotic shifts due to rapid changes in plasma glucose is very rare in ketoacidosis, and thus the safety of using 0.1 unit/kg/h outweighs any risk.

2.7 | Complications of ketoacidosis and its treatment

1. Hypokalaemia and hyperkalaemia

Due to the dehydration, lack of insulin and metabolic acidosis, hyperkalaemia should be sought when ketoacidosis is initially diagnosed. In a UK national survey 283 people treated with the 2013 edition of this guideline, the mean (\pm SD) admission potassium was 4.8 (\pm 1.0) mmol/L.⁴⁵ Hypokalaemia and hyperkalaemia are potentially life-threatening conditions during the management of ketoacidosis. Because of the risk of acute pre-renal kidney injury associated with severe dehydration, it is recommended that no potassium be prescribed with the initial fluid resuscitation or if the serum potassium level remains above 5.5 mmol/L. A normal or even elevated serum potassium concentration may be seen due to the extracellular shift of potassium in acidotic conditions, and this very poorly reflects total potassium stores. However, potassium will almost always fall as the ketoacidosis is treated with

insulin and the UK survey showed that 67.1% developed hypokalaemia (<4.0 mmol/L) at 24 h after admission.⁴⁵

Thus it is recommended that 0.9% sodium chloride solution with potassium 40 mmol/L (ready-mixed) is prescribed as long as the serum potassium level is below 5.5 mmol/L and the person is passing urine. If the serum potassium level falls below 3.5 mmol/L the potassium regimen needs review. Where the fluid balance permits, an increase in the rate of the infusion of 0.9% sodium chloride solution with potassium 40 mmol/L is possible. Otherwise, a more concentrated potassium infusion will be needed and to ensure safe practice, all aspects of its use must comply with local and national guidance.^{50,51}

In addition to inadequate replacement, the main driver for hypokalaemia is the use of insulin. Thus, when glucose drops below 14 mmol/L, consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/h.

Trusts need to ensure that they have local protocols in place, which allow for the safe administration of concentrated potassium solutions. This may require transfer to a Level 2 or Level 3 environment.

2. Hypoglycaemia

The BG may fall very rapidly as ketoacidosis is corrected and a common mistake is to allow the BG to drop to hypoglycaemic levels. In the UK national survey of 283 people treated with the 2013 edition of this guideline, glucose dropped to <4.0 mmol/L in 27.6% of people.⁴⁵ Severe hypoglycaemia (i.e., requiring third-party assistance) is also associated with increased length of stay, cardiac arrhythmias, acute brain injury and death.⁵² The main driver for hypoglycaemia is the use of insulin. Thus, in addition to commencing 10% dextrose to run alongside the 0.9% sodium chloride solution, when glucose drops below 14 mmol/L, consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/h.

3. Cerebral oedema

Cerebral oedema causing symptoms is relatively uncommon in adults, although may occur in those who are physically slight or in younger adults. Asymptomatic cerebral oedema may be a common occurrence, and may exist prior to treatment starting.^{24,53} The exact cause of this phenomenon is unknown. Reassuringly a large randomised controlled trial of 0.9% sodium chloride solution versus 0.45% sodium chloride solution each given either rapidly or slowly, showed no differences in the rates of developing neurological injury.⁴⁰ It is thus possibly an idiosyncratic response to the metabolic injury and subsequent treatment. However, any deterioration in Glasgow Coma Scale score should prompt urgent treatment and imaging. If cerebral oedema is suspected, urgent treatment with mannitol or hypertonic saline to induce osmotic fluid shifts should be started and not be delayed while awaiting imaging.²⁴

4. Other complications

Several other complications may occur with some being relatively common, generally mild and easily treated. However, others may be more serious. These include the development of venous thromboembolic disease, particularly if central venous catheters are used. Transient acute kidney injury may occur in up to 50% of adults.²⁴ Other, rare complications include pulmonary oedema; a rise in pancreatic enzymes, with or without acute pancreatitis; cardiomyopathy; rhabdomyolysis; and gastrointestinal bleeding.²⁴

2.8 | The management of ketoacidosis in people with end-stage renal failure or on dialysis

Fortunately, this is a relatively rare occurrence. There are limited data on the management of ketoacidosis in this circumstance.^{54–57} The lack of renal insulin clearance means that ketoacidosis is much less likely to occur. It may also be difficult to determine because of the chronic metabolic acidosis associated with advanced chronic kidney disease (stages 4 and 5). Recent data suggest that those presenting in ketoacidosis with end-stage renal disease have lower β -hydroxybutyrate concentrations, and higher glucose and anion gap than those with preserved renal function.⁵⁸ Bicarbonate and pH were not significantly different.⁵⁸ When ketoacidosis does occur in end-stage renal disease, several issues need to be considered.

2.8.1 | Fluid replacement

The inability to develop an osmotic diuresis means that dialysis-associated hyperglycaemia and ketosis can occur without much dehydration. A mixed picture of ketoacidosis and hyperglycaemic hyperosmolar state may also occur because of the high serum tonicity.⁵⁶ In addition, the circulating intravascular volume may increase at the expense of intracellular volume that resolves as the glucose and ketosis normalises. Therefore, there may be no need for fluid replacement in those with end-stage renal failure or those on dialysis. However, for those who are deemed hypovolaemic, aliquots of 250 ml (0.9% sodium chloride or 10% dextrose) may be given with frequent clinical assessments.

2.8.2 | Insulin treatment

For people with end-stage renal failure or those on dialysis, insulin replacement is the mainstay of treatment. This should be given as an FRIII at an initial rate of 0.1 units/kg/h,

but may need to increase if the required rate of glucose fall is not achieved. However, the failure to renally clear insulin increases the risk of hypoglycaemia. However, the rate of glucose reduction is the same as for people with preserved renal function—that is, 3.0 mmol/L/h. If the rate of fall is faster, or the glucose falls to <14.0 mmol/L strongly consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/h.

2.8.3 | Potassium

Potassium supplementation is not usually required because the lack of the osmotic diuresis means that there is significantly less potassium loss than for those with preserved renal function. However, the acidosis may lead to significant hyperkalaemia, and this is more common in those with renal failure.⁵⁴ In this circumstance, continuous cardiac monitoring is essential and critical care or the specialist renal team should be involved to consider urgent haemodialysis/haemofiltration.

3 | KETOACIDOSIS PATHWAY OF CARE

Ketoacidosis is a medical emergency with a significant morbidity and mortality. It should be diagnosed promptly and managed intensively. The specialist diabetes team should always be involved as soon as possible and ideally within 24 h because this has been demonstrated to be associated with a better experience for the PWD and reduced length of stay.⁵⁹

Where young people aged 16–18 years are managed by adult medical teams because of local arrangements, it is considered appropriate for them to be managed using local adult guidelines that the teams are familiar with rather than using potentially unfamiliar paediatric guidelines.

Where individuals aged 16–18 are managed by paediatric teams, the paediatric guidelines should be followed.

3.1 | Assessment of severity

The presence of one or more of the following may indicate severe ketoacidosis:

- Blood ketones over 6.0 mmol/L
- Bicarbonate level below 5.0 mmol/L
- Venous/arterial pH below 7.0
- Hypokalaemia on admission (under 3.5 mmol/L)
- GCS less than 12 or abnormal AVPU scale
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)

- Systolic BP below 90 mm Hg
- Pulse over 100 or below 60 bpm
- Anion gap above 16 [Anion Gap = $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$]

If the individual exhibits any of these signs, resuscitation and treatment should be started without delay, and an intensive monitoring regimen put in place. Depending on local circumstances individuals who fulfil the criteria for severity or who require intensive monitoring should be reviewed by a consultant physician and considered for swift referral to a Level 2/HDU (High Dependency Unit) environment, or if the individual has failed to improve after initial resuscitation measures.⁶⁰ It may also be necessary to consider a surgical cause for the deterioration. If surgery is required, there will need to be an urgent senior multidisciplinary discussion on the optimum time to operate.

In those using an insulin pump, if transfer to a Level 2/HDU or ITU is necessary, then the pump should be stopped, removed and stored safely.

The use of flash glucose monitoring (e.g., Freestyle Libre®, Dexcom G6®, etc) in these circumstances is not known. Further work is necessary to determine their utility in critical illness. Until such data are available, they may be left on, but data from them should not be used to guide treatment.

Example intravenous insulin prescription and fluid protocol are shown in Appendix 2.

4 | 0–60 min: IMMEDIATE MANAGEMENT ON DIAGNOSIS

T = 0 at time intravenous fluids are commenced. If there is a problem with intravenous access, critical care support should be requested immediately.

4.1 | Aims

- Commence IV 0.9% sodium chloride solution
- Commence an FRIII, but only after fluid therapy has been commenced
- Establish monitoring regime appropriate for the PWD; generally hourly BG and hourly ketone measurement, with at least 2 hourly serum/blood potassium and bicarbonate for the first 6 h
- Clinical and biochemical assessment of the individual
- Involve the diabetes specialist team at the earliest possible stage
- Consider referral to a Level 2/HDU environment if criteria for severity are met or if facilities for intensive monitoring are unavailable

4.2 | Action 1—Intravenous access and initial investigations

- Rapid ABC (Airway, Breathing, Circulation)
- Large bore IV cannula and commence IV fluid replacement (See Action 2)
- Clinical assessment
- Respiratory rate, temperature, blood pressure, pulse, oxygen saturation
- Glasgow Coma Scale. N.B.: a drowsy individual in the context of ketoacidosis is seriously concerning, and the person requires critical care assessment. Consider an NG tube with airway protection to prevent aspiration
- Full clinical examination

Initial investigations should include the following:

- Blood ketones
- Capillary BG
- Venous plasma glucose
- Urea and electrolytes (including phosphate if necessary)
- Venous blood gases
- Full blood count
- Blood cultures (if infection is suspected)
- ECG
- Chest radiograph if clinically indicated
- Urinalysis and culture
- Continuous cardiac monitoring
- Continuous pulse oximetry
- Consider precipitating causes and treat appropriately
- Establish usual medication for diabetes
- Pregnancy test in women of child-bearing age
- COVID-19 testing—particularly in those not known to have a prior diagnosis of diabetes

4.3 | Action 2—Restoration of circulating volume

Assess the severity of dehydration using pulse and blood pressure. As a guide, 90 mm Hg may be used as a measure of hydration but take age, gender and concomitant medication into account.

4.3.1 | Systolic BP on admission below 90 mm Hg

Hypotension is likely to be due to low circulating volume, but consider other causes such as heart failure and sepsis.

- Give 500 ml of 0.9% sodium chloride solution over 10–15 min. If systolic BP (SBP) remains below 90 mm Hg,

this may be repeated while awaiting senior input. In practice most individuals require between 500 and 1000 ml given rapidly.

- If there has been no clinical improvement reconsider other causes of hypotension and seek an immediate senior assessment. Consider involving the ITU/critical care team.
- Once SBP above 90 mm Hg follow fluid replacement as shown below.

4.3.2 | Systolic BP on admission 90 mm Hg and over

Table 4 outlines a typical fluid replacement regimen for a previously well 70 kg adult. This is an illustrative guide only. A slower infusion rate should be considered in young adults (see Controversial Areas).

4.4 | Exercise caution in the following groups:

- Young people aged 18–25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities

In these situations admission to a Level 2/HDU facility should be considered. Fluids should be replaced cautiously.

4.5 | Action 3—Potassium replacement

Hypokalaemia and hyperkalaemia are life-threatening conditions and are common in ketoacidosis. Serum potassium is often high on admission (although total body

potassium is low) but falls precipitously on treatment with insulin. Regular monitoring is mandatory (Table 5).

4.6 | Action 4—Commence a fixed-rate intravenous insulin infusion

- If the person is unable to state their weight, or it is not available, estimate it in kilograms
- If it is a pregnant woman, use her present weight and call for immediate additional senior obstetric help
- Start a continuous FRIII via an infusion pump. This is made of 50 units of human-soluble insulin (Actrapid[®], Humulin S[®]) made up to 50 ml with 0.9% sodium chloride solution. Ideally, this should be provided as a ready-made solution
- Infuse at a fixed rate of 0.1 unit/kg/hr (i.e. 7 ml/h if weight is 70 kg) (see Table 3)
- Only give a bolus (stat) dose of intramuscular insulin (0.1 unit/kg) if there is a delay in setting up an FRIII
- If the individual normally takes long-acting basal insulin (e.g., glargine, degludec, detemir or human isophane insulin) continue this at the usual dose and usual time
- Insulin may be infused in the same line as the intravenous replacement fluid provided that a Y connector with a one-way, anti-siphon valve is used and a large-bore cannula has been placed. However, two large bore intravenous catheters are advisable

TABLE 5 The suggested potassium replacement regimen

Potassium level in first 24 h (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5–5.5	40
Below 3.5	Senior review as additional potassium needs to be given (see serious complications section)

TABLE 4 An outline of a typical fluid replacement regimen for a previously well 70 kg adult

Fluid	Volume
0.9% sodium chloride 1 L ^a	1000 ml over first hour
0.9% sodium chloride 1 L with potassium chloride	1000 ml over next 2 h
0.9% sodium chloride 1 L with potassium chloride	1000 ml over next 2 h
0.9% sodium chloride 1 L with potassium chloride	1000 ml over next 4 h
0.9% sodium chloride 1 L with potassium chloride	1000 ml over next 4 h
0.9% sodium chloride 1 L with potassium chloride	1000 ml over next 6 h

Note: Re-assessment of cardiovascular status at 12 h is mandatory, further fluid may be required.

^aPotassium chloride may be required if more than 1 L of sodium chloride has been given already to resuscitate those who are hypotensive.

5 | 60 min–6 h

5.1 | Aims

- Clear the blood of ketones and suppress ketogenesis
- Achieve a rate of fall of ketones of at least 0.5 mmol/L/h
- In the absence of ketone measurement, bicarbonate should rise by 3.0 mmol/L/h and BG should fall by 3.0 mmol/L/h
- Maintain serum potassium in the normal range
- Avoid hypoglycaemia
- Consider referral to a Level 2 (HDU) environment if criteria for severity are met after initial resuscitation or if facilities for intensive monitoring are unavailable

5.2 | Action 1—Re-assess and monitor vital signs

- During this time, individuals should be reviewed hourly initially to ensure that adequate progress is being made in reducing the ketone and/or glucose concentrations
- Consider urinary catheterisation if the person is incontinent or anuric (i.e., not passed urine by 60 min)
- Consider naso-gastric tube insertion if the person is obtunded or persistently vomiting
- If the oxygen saturation falls, then perform an arterial blood gas measurement and request a repeat chest radiograph
- Regular observations and Early Warning Score (EWS) charting as appropriate
- Regular assessment of Glasgow Coma Scale score, if this drops then urgent brain imaging should be considered
- Maintain an accurate fluid balance chart, the minimum urine output should be no less than 0.5 ml/kg/h
- Continuous cardiac monitoring in those with severe ketoacidosis
- Give prophylactic low-molecular-weight heparin as per NICE guidance⁶¹

5.3 | Action 2—Review metabolic parameters

- Measure blood ketones and capillary glucose hourly (Note: if meter reads 'BG over 20 mmol/L' or 'Hi' venous blood should be sent to the laboratory hourly or measured using venous blood in a blood gas analyser until the point-of-care testing meter is within its QA range)
- The hourly glucose readings should be recorded directly into the hospital pathology system. Where this is not

possible (e.g., with non-networked glucose meters), the results should be recorded in the notes

- Review the response to FRIII hourly by calculating the rate of change of ketone level fall (or rise in bicarbonate or fall in glucose)
- Assess the resolution of ketoacidosis
 - a. If blood ketone measurement is available and blood ketones are not falling by at least 0.5 mmol/L/h, call a prescribing clinician to increase the insulin infusion rate by 1.0 unit/h increments hourly until the ketones are falling at target rates (also check infusion)*
 - b. If blood ketone measurement is not available, use venous bicarbonate. If the bicarbonate is not rising by at least 3.0 mmol/L/h call a prescribing clinician to increase the insulin infusion rate by 1 unit/h increments hourly until the bicarbonate is rising at this rate*
 - c. Alternatively use plasma glucose. If the glucose is not falling by at least 3.0 mmol/L/h call a prescribing clinician to increase the insulin infusion rate by 1.0 unit/hr increments hourly until glucose falls at this rate. Glucose level is not an accurate indicator of resolution of acidosis in ketoacidosis, so the acidosis resolution should be verified by venous gas analysis*
- Measure venous blood gas for pH, bicarbonate and potassium at 60 min, 2 h and 2 hourly thereafter
- If the potassium is outside the reference range (4.0–5.5 mmol/L), assess the appropriateness of the potassium replacement and check it hourly. If it remains abnormal after a further hour, seek immediate senior medical advice (see Action 3)
- Continue the FRIII until the ketone measurement is less than 0.6 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L (see section C)
- Do not rely on urinary ketone clearance to indicate resolution of ketoacidosis because these will still be present when the ketoacidosis has resolved¹⁴
- If the glucose falls below 14.0 mmol/L, commence 10% glucose given at 125 ml/h alongside the 0.9% sodium chloride solution. In addition, consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/h.
- Monitor and replace potassium because it may fall rapidly**

* If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction).

**NB: The intravenous insulin and the dextrose infusions should be infused using a Y connector.

5.4 | Action 3—Identify and treat precipitating factors

5.5 | Action 4—Use of long acting insulin

Those presenting with newly diagnosed diabetes should be given long-acting basal insulin (e.g., glargine, detemir or degludec—or human NPH insulin, depending on local policy) at a dose of 0.25 units/kg subcutaneously once daily to mitigate against rebound ketosis when they are taken off the FRIII.⁶²

6 | 6–12 h

6.1 | Aim

The aim within this time period is to do the following:

- Ensure that clinical and biochemical parameters are improving at the correct rates
- Continue IV fluid replacement
- Continue insulin administration
- Assess for complications of treatment, for example, fluid overload, cerebral oedema
- Continue to treat precipitating factors as necessary
- Avoid hypoglycaemia
- Consider referral to a Level 2 (HDU) environment if criteria for severity are met despite adequate treatment, or if there is a deterioration in clinical status or if facilities for intensive monitoring are unavailable

6.2 | Action 1—Re-assess the individual and monitor vital signs

- If the person is not improving as expected then seek early senior advice
- Regular assessment of Glasgow Coma Scale score, if this drops then urgent brain imaging should be considered
- Ensure a referral has been made to the specialist diabetes team
- Consider referral to a Level 2 (HDU) environment if criteria for severity are met or if facilities for intensive monitoring are unavailable

6.3 | Action 2—Review biochemical and metabolic parameters

- At 6 h check the venous pH, bicarbonate, potassium, as well as blood ketones and glucose

- Resolution of ketoacidosis is defined as ketones less than 0.6 mmol/L and venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage because the hyperchloraemic acidosis associated with large volumes of 0.9% sodium chloride will lower bicarbonate levels)

If ketoacidosis has resolved, go to section E.

If ketoacidosis has not resolved, refer to Action 2 in Section B.

7 | 12–24 h

7.1 | Expectation

By 24 h, the ketonaemia and acidosis should have resolved in most people⁴⁵

7.2 | Aim

- Ensure that the clinical and biochemical parameters are improving or have normalised
- Continue IV fluids if the person is not eating and drinking
- If the person is not eating and drinking and there is no ketonaemia move to a VRIII as per local guidelines or following the JBDS guideline⁶³
- Re-assess for complications of treatment, for example, fluid overload
- Regular assessment of Glasgow Coma Scale score, if this drops then urgent brain imaging should be considered
- Continue to treat any precipitating factors as necessary
- Transfer to subcutaneous insulin if the individual is eating and drinking normally. Ensure that the subcutaneous insulin is started before the IV insulin is discontinued. Ideally, give the subcutaneous fast-acting insulin at a meal and discontinue IV insulin 30–60 min later

7.3 | Action 1—Re-assess the individual and monitor vital signs

7.4 | Action 2—Review the biochemical and metabolic parameters

- At 12 h check venous pH, bicarbonate, potassium, as well as blood ketones and glucose
- Resolution of ketoacidosis is defined as ketones less than 0.6 mmol/L, and venous pH over 7.3

If ketoacidosis resolved, go to section E.

If ketoacidosis has not resolved, refer to Action 2 in Section B and seek senior specialist advice as a matter of urgency.

7.4.1 | Why the bicarbonate cannot be relied on to assess the resolution of DKA

Do not rely on bicarbonate alone to assess the resolution of ketoacidosis at this point due to the possible hyperchloraemia secondary to high volumes of 0.9% sodium chloride solution which also contain potassium chloride. The hyperchloraemic metabolic acidosis will lower the bicarbonate and thus lead to difficulty in assessing whether the ketosis has resolved. The hyperchloraemic acidosis may cause renal vasoconstriction and be a cause of oliguria.

7.4.2 | Expectation

People who have had ketoacidosis should be eating and drinking and back on their normal insulin regimen. If this expectation is not met within this time period, it is important to identify and treat the reasons for the failure to respond to treatment—for example, gastritis. It is unusual for ketoacidosis not to have biochemically resolved by 24 h with appropriate treatment and, if encountered, requires senior diabetes specialist input.

7.5 | E. Conversion to subcutaneous insulin

The PWD should be converted to an appropriate subcutaneous regimen when biochemically stable (blood ketones less than 0.6 mmol/L, pH over 7.3) and they are ready and able to eat.⁶³ Conversion to subcutaneous insulin is ideally managed by the diabetes specialist team. If the team is not available see Appendix 1. If the PWD is newly diagnosed, it is essential they are seen by a member of the specialist team prior to discharge.

7.6 | Specialist diabetes team input

If they are not already involved, the local diabetes team should be informed and the PWD reviewed within 24 h of admission. Diabetes team input is important to allow re-education, to reduce the chance of recurrence, and to facilitate appropriate follow-up. Hospitals should enable diabetes teams to provide sufficient cover to allow anyone admitted with ketoacidosis to be reviewed within 24 h of admission.

8 | PATHOPHYSIOLOGY OF KETOACIDOSIS

Ketoacidosis is a complex disordered metabolic state characterised by hyperglycaemia, ketonaemia and acidosis. Ketoacidosis usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter regulatory hormones (i.e., glucagon, cortisol, growth hormone, catecholamines). This type of hormonal imbalance enhances hepatic gluconeogenesis and glycogenolysis resulting in severe hyperglycaemia. Enhanced lipolysis increases serum free fatty acids that are then metabolised as an alternative energy source in the process of ketogenesis.²⁴ This results in accumulation of large quantities of ketone bodies and subsequent metabolic acidosis. Ketones include acetone, 3-beta-hydroxybutyrate and acetoacetate. The predominant ketone in the blood is 3-beta-hydroxybutyrate.¹⁴ A more detailed description of the pathophysiology of ketoacidosis is available elsewhere.²⁴

There are several mechanisms responsible for fluid depletion in ketoacidosis. These include osmotic diuresis due to hyperglycaemia, vomiting - commonly associated with ketoacidosis - and eventually, inability to take in fluid due to a diminished level of consciousness. Electrolyte shifts and depletion are in part related to the osmotic diuresis. Hyperkalaemia and hypokalaemia need particular attention.

9 | EPIDEMIOLOGY AND COST

Although ketoacidosis occurs predominantly in people with type 1 diabetes, about a third of cases occur in people with type 2 diabetes.^{23,64} However, the initial treatment is the same for both. The true incidence is difficult to establish. In the United Kingdom, the incidence of ketoacidosis was highest in those aged 18 to 24 years old.²³ Other data have suggested that the incidence of ketoacidosis ranges between 8.0 and 51.3 cases per 1000 patient-years in people with type 1 diabetes.⁶⁵ However, in China, the incidence has been reported to be as high as 263 per 1000 patient-years.^{66,67} Ketoacidosis is also an expensive condition to treat. Data from national surveys in the United Kingdom show that the cost of one episode is estimated to cost £2064 in adults and £1387 in those aged 11 to 18 years.^{68,69} Treating ketoacidosis in the United States is significantly more expensive with a single episode estimated to cost ~\$26,566.⁷⁰

10 | MORTALITY AND MORBIDITY

In the United Kingdom and other developed nations, while the mortality from ketoacidosis remains <1%,^{45,71} it is the leading cause of death among people under 58 years old with T1DM.⁷² Unsurprisingly perhaps, mortality increases with age and with the presence of pre-existing comorbidities.^{73,74}

The mortality rate is still high at more than 40% in some low- and middle-income countries.²⁴ This high mortality rate illustrates the necessity of early diagnosis and the implementation of effective prevention programmes.

Cerebral oedema remains the most common cause of mortality, particularly in young children and adolescents. The main causes of mortality in the adult population include severe hypokalaemia, adult respiratory distress syndrome and co-morbid states, which may have precipitated the ketoacidosis such as pneumonia, acute myocardial infarction and sepsis.²⁴

11 | IMPLEMENTATION OF THE GUIDELINES

Repeated audits by many diabetes units in all constituent UK countries have consistently demonstrated poor adherence to local (or national) guidelines in the management of ketoacidosis. There are two main problems to be addressed:

1. The guidelines must be implemented
2. The guidelines must be audited—The audit criteria can be found on line.

The guidelines must be reviewed regularly. This is a 'live' document and feedback to the authors is welcomed and encouraged.

12 | COMMISSIONING OF CARE

Ketoacidosis is a common medical emergency and must be treated appropriately. For this to occur, the Health Economies within the United Kingdom must address management of ketoacidosis in the context of provision of expert medical and nursing input within secondary care. In the majority of cases, people with type 1 diabetes should be under specialist care. Commissioners, Primary Care Providers, Local Diabetes Networks and Diabetes Directorates within the Acute Trusts, should co-operate and ensure the Quality Indicators and Audit Standards set out below are met.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

KD is the main author on behalf of the Joint British Diabetes Society for Inpatient Care.

ORCID

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Dhatariya KK; The Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults—An updated guideline from the Joint British Diabetes Society for Inpatient Care. *Diabet Med*. 2022;00:e14788. doi:[10.1111/dme.14788](https://doi.org/10.1111/dme.14788)

APPENDIX 1

Restarting subcutaneous insulin for those already established on insulin

The person's previous regimen should generally be restarted if their most recent HbA_{1c} suggests acceptable level of control, that is, HbA_{1c} <64 mmol/mol (<8.0%)⁶³

With all regimens, the intravenous insulin infusion should not be discontinued for at least 30–60 min after the administration of the subcutaneous dose given in association with a meal.

If they were on basal bolus insulin

- There should be an overlap between the insulin infusion and first injection of fast-acting insulin. The fast-acting insulin should be injected with the meal and the intravenous insulin and fluids discontinued 30–60 min later
- If the person was previously on a long-acting insulin such as glargine, degludec, detemir or human isophane, this should have been continued and thus the only action should be to restart their normal, short-acting insulin at the next meal
- If the basal insulin had been stopped in error, the insulin infusion should not be stopped until some form of background insulin has been given. If the basal insulin was normally taken once daily in the evening and the intention is to convert to subcutaneous insulin in the morning, give half the usual daily dose of basal insulin as isophane (i.e. Insulatard[®], Humulin I[®], Insuman basal[®]) in the morning. This will provide essential background insulin until the long-acting analogue can be recommenced. Check the blood ketone and glucose levels regularly

If they were on twice daily fixed-mix insulin

- Re-introduce the subcutaneous insulin before breakfast or before the evening meal. Do not change at any other

time. Maintain the insulin infusion for 30–60 min after the subcutaneous insulin was given

If they were on CSII

- Ensure the availability of necessary supplies/ and or consumables
- Ensure that the individual has been assessed as being able to use the CSII
- If they are deemed as able to use the pump, recommence the CSII at the usual basal rate. Continue intravenous insulin infusion until the meal bolus has been given. Do not recommence CSII at bedtime

Calculating the subcutaneous insulin dose in those who are insulin-naïve

Estimate total daily dose of insulin

This estimate is based on several factors, including the PWD sensitivity to insulin, degree of glycaemic control, insulin resistance, weight and age. The TDD can be calculated by multiplying the individual's weight (in kg) by 0.5–0.75 units. Use 0.75 units/kg for those thought to be more insulin resistant, that is, teens, obese.

Example:

A 72-kg person would require approximately 72×0.5 units or 36 units in 24 h.

Calculating a basal bolus (QDS)

Regimen

Give 50% of total dose with the evening meal in the form of long-acting insulin, and divide remaining dose equally between pre-breakfast, pre-lunch and pre-evening meal.

	Pre-breakfast	Pre-lunch	Pre-evening meal	Bedtime
Rapid-acting insulin, e.g. aspart (e.g., Novorapid [®])/glulisine (e.g., Apidra [®])/lispro (e.g., Humalog [®])	6 units	6 units	6 units	
Long-acting insulin, e.g., glargine (e.g., Lantus [®]), detemir (e.g., Levemir [®]) or degludec (e.g., Tresiba [®])			18 units	

Administer the first dose of fast-acting subcutaneous insulin preferably prior to breakfast or lunch. Only administer the first dose before the evening meal if appropriate monitoring can be guaranteed. Do not convert to a subcutaneous regimen at bedtime.

In those new to insulin therapy, dose requirements may decrease within a few days because the insulin resistance associated with ketoacidosis resolves.

Close supervision from the diabetes specialist team is required.

Calculating a twice-daily (BD) regimen:

If a twice-daily, pre-mixed insulin regimen is to be used, give two thirds of the total daily dose at breakfast, with the remaining third given with the evening meal.