Management of diabetic ketoacidosis: a summary of the 2013 Joint British Diabetes Societies guidelines 1A02, 2C04

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The purpose of this article is to summarise and to highlight the key points for intensivists from the revised Joint British Diabetes Societies (JBDS) guidelines on the management of diabetic ketoacidosis, which have been endorsed by the Intensive Care Society. Highlights include the following: the use of weight-based fixed-rate intravenous insulin infusion (FRIII); bedside measurement of capillary ketones to monitor response to treatment; use of 0.9% saline with premixed potassium chloride as the main resuscitation fluid on the general medical ward (balanced crystalloids are permitted in intensive care areas where concentrated potassium chloride may be added); hourly measurement of capillary blood glucose; adding 10-20% glucose when the blood glucose falls below 14 mmol/L; continuation of long-acting insulin analogues if the patient is already taking these and referral to intensive care if the patient meets certain criteria. The rationale and the goals of the JBDS guidelines are also described.

Keywords: *diabetic ketoacidosis; intensive care; practice guidelines, adult*

Introduction

Diabetic ketoacidosis (DKA) is a severe and common life-threatening complication of type 1 diabetes and ketone-prone type 2 diabetes; it frequently necessitates intensive care admission. In England in 2010, there were 14,375 admissions to acute NHS hospitals where DKA was the primary diagnosis. Data from The Intensive Care National Audit and Research Centre (ICNARC) shows that there are about 1,800 annual admissions to intensive care with a diagnosis of DKA. Therefore, approximately 13% of the patients admitted with DKA to acute hospitals in England are subsequently admitted to an intensive care unit (ICU). Furthermore, data from the 13 ICUs in the East of England suggest that DKA is the primary diagnosis in 2% of adult patients admitted to general intensive care units.[1]

The Joint British Diabetes Societies (JBDS) perceived that the lack of consistent and current guidance may contribute to the morbidity and mortality associated with DKA. To overcome these concerns, in March 2010 the JBDS published guidelines for the management of DKA in adults.[2] The main points of these guidelines include:

- The use of a weight-based fixed-rate intravenous (IV) insulin infusion (FRIII).
- Use of bedside measurement of capillary ketones using a hand-held meter to monitor response to treatment.
- Use of 0.9% saline as the main resuscitation fluid, adding 10% glucose when the blood glucose falls below 14 mmol/L, in order to allow the FRIII to be continued.
- Continuation of long-acting insulin analogues such as insulin glargine (Lantus®) and insulin detemir (Levemir®), if the patient is already taking these.
- Referral for consideration of intensive care if the patient meets certain criteria.

Subsequently, the National Inpatient Diabetes Audit of 2012 showed that 170 hospitals in the UK have produced new DKA guidelines and these hospitals have either adopted or modified the JBDS guidelines for local use.[3] One of the criticisms levelled at the JBDS was that despite DKA often necessitating intensive care admission, the guidelines were produced without consultation with the intensive care community.[1]

In September 2013, the JBDS published the second edition[4] with changes, including the addition of criteria to define the resolution of DKA and the option to continue human basal insulins in patients. The JBDS asked the Intensive Care Society (ICS) to review and contribute to the document and the ICS endorsed the new guidelines.

The guideline has several sections. These include:

1. Rationale for best practice
2. Controversial areas
3. Serious complications of DKA and its treatment
4. DKA pathway of care
5. Implementation and audit
6. References
7. Appendices.

The purpose of this article is to summarise and to highlight the key points from the ICS-endorsed guidelines that are pertinent to intensivists.

Rationale for best practice

The accepted diagnostic criteria for diabetic ketoacidosis is the triad of:

- ketonaemia >3.0 mmol/L or significant ketonuria
- blood glucose >11 mmol/L or known diabetes mellitus
- plasma bicarbonate <15 mmol/L and/or venous pH <7.3.

Pathophysiology of DKA

Diabetic ketoacidosis is a complex disordered metabolic state characterised by hyperglycaemia, acidosis, and ketonaemia; it usually occurs as a consequence of relative or absolute insufficiency of insulin and the consequent imbalance of other hormones. The lack of insulin, and the rise in counterbalance hormones such as cortisol and glucagon, result in significant hyperglycaemia via increased hepatic gluconeogenesis and glycogenolysis, with reduced peripheral glucose uptake. Increased lipolysis gives rise to free fatty acids that are converted to ketone bodies in the liver, including acetone, β-hydroxybutyrate, and acetoacetate. The predominant ketone in DKA is β-hydroxybutyrate. The ketones contribute to metabolic acidosis. The metabolic acidosis is further compounded by hypovolaemia caused by osmotic diuresis; vomiting; and reduced fluid intake.

The involvement of diabetes specialist teams

The diabetes specialist team must always be involved in the care of patients admitted to hospital with DKA. Their involvement shortens length of stay and improves safety. The principles of optimal transition from intravenous insulin infusions to subcutaneous insulin are discussed in Appendix 1 of the guidelines, however a specialist in diabetes will personalise the regime.

Controversial topics

The authors of the guidelines acknowledge that there are controversies in the optimal management of DKA. The guidelines discuss the following topics in detail.

1. Venous blood can be used for measurement of pH and bicarbonate (rather than arterial blood) on the general medical ward
2. Blood ketone meters should be used for near-patient testing
3. Crystalloid rather than colloid solutions are recommended for fluid resuscitation
4. Fluid replacement in young adults should be cautious
5. The recommended fluid of choice is 0.9% sodium chloride solution on the general medical wards; it is recommended because it is commercially available with premixed potassium chloride, and therefore complies with National Patient Safety Agency (NPSA) recommendations
6. Subcutaneous long-acting analogue/human insulin should be continued
7. Insulin should be administered as a FRIII, calculated on body weight
8. There is no requirement for a loading dose of insulin
9. Bicarbonate administration is not recommended routinely
10. Phosphate should not be supplemented routinely
11. The ideal rate of glucose lowering is discussed.

Resuscitation fluids for DKA

Saline 0.9% has been the preferred fluid for resuscitation of DKA by physicians. Recent evidence suggests a faster resolution of the acidosis occurs when a balanced fluid is used.[5] However, only 0.9% saline is commercially available with either 0.15% or 0.3% potassium chloride. Thus, to ensure compliance with NPSA recommendations, 0.9% saline remains the fluid of choice on the wards. However, in intensive care as it is possible to both add concentrated potassium chloride to Hartmann's solution, or to infuse concentrated potassium chloride centrally, thus intensivists may choose to use a balanced solution such as Hartmann's solution. The JBDS guidelines acknowledge this disparity.

Marker for guiding IV insulin therapy

Classically, capillary blood glucose (CBG) levels have been used to guide insulin therapy. It is now recognised that CBGs are a poor surrogate marker for the resolution and cessation of the ketotic process. The practice of using CBGs as the surrogate marker to guide DKA treatment has contributed to the clinical scenario whereby the insulin infusion is reduced/stopped as the CBG falls, while the patient is still profoundly acidotic/ketotic. With the recent advent of bedside ketone meters, it is now recommended that β-hydroxybutyrate should be used as the marker to guide intravenous insulin treatment.

Administration of IV insulin

To ensure resolution of ketosis the current consensus is that a fixed-rate IV insulin infusion (FRIII) should be administered until the ketone levels are less than 0.6 mmol/L. The FRIII should be administered at a rate of 0.1 unit/kg/hr of short-acting human soluble insulin (Actrapid® or Humulin S®) until resolution of ketosis, with a maximum rate of 15 unit/hour. The FRIII should be continued until the bedside capillary ketone levels are less than 0.6 mmol/L, the pH >7.3 and the patient has been started on an alternative insulin.

A legitimate concern with the use of the continuous FRIII is that dangerous hypoglycaemia may result. It is therefore imperative that hourly monitoring of the CBG is performed, and that IV glucose is administered once the CBG is less than 14 mmol/L. This will also necessitate re-evaluation of other fluids to ensure that fluid overload does not ensue.

Continuation of basal insulins

The 2010 guidelines recommended the continuation of only the subcutaneous long-acting basal insulin analogues (Levemir®, Lantus®). This is because continuation of subcutaneous analogues provides background insulin when the IV insulin is discontinued, thus avoiding rebound hyperglycaemia when the intravenous insulin is stopped. It is suggested that this strategy may reduce the length of hospital stay. The recent 2013 guidelines suggest consideration of continuation of human basal insulins (Humulin I®, Insulatard®, Insuman Basal®). This is because some units have continued these human basal insulins with no apparent problems.

Serious complications of DKA or its treatment

The guidelines discusses hypokalaemia and hyperkalaemia; hypoglycaemia; cerebral oedema and pulmonary oedema, in detail. As previously discussed, hypoglycaemia is a real concern with the FRIII, and thus hourly CBG is mandatory to allow

	0-60 minutes	60 minutes to 6 hours	6-12 hours	12 -24 hours
Aims	• Commence IV 0.9% sodium chloride solution • Start an FRIII but only after fluid therapy has been commenced • Establish monitoring regime appropriate to patient • Clinical and biochemical assessment of the patient • Involve the diabetes specialist team at the earliest possible stage	• Clear the blood of ketones and suppress ketogenesis • Achieve a rate of fall of ketones >0.5 mmol/L/hr • Aim for bicarbonate to rise by 3.0 mmol/L/hr • Aim for CBG to fall by 3.0 mmol/L/hr • Maintain serum potassium in the normal range • Avoid hypoglycaemia	• Ensure that clinical and biochemical parameters are improving • Continue IV fluid replacement • Continue insulin administration • Assess for complications of treatment eg, fluid overload, cerebral oedema • Continue to treat precipitating factors as necessary • Avoid hypoglycaemia	• Ensure that clinical and biochemical parameters have normalised • Continue IV fluids if the patient is not eating and drinking • If the patient is not eating and drinking and there is no ketonaemia move to a VRIII as per local guidelines • Re-assess for complications of treatment • Continue to treat any precipitating factors • Transfer to normal subcutaneous insulin if the patient is eating and drinking normally
Actions	• Initial assessment and simultaneous resuscitation • Restoration of circulating volume • Potassium replacement when indicated • Commence a FRIII	• Re-assess patient, monitor vital signs • Review metabolic parameters • Identify and treat precipitating factors • Administer long-acting insulin	• Re-assess patient, monitor vital signs • Review metabolic parameters	• Re-assess patient, monitor vital signs • Review metabolic parameters • Involve the diabetes team

Table 1 Summary of the aims and actions in the DKA pathway.
Key: FRIII: fixed rate intravenous insulin infusion, CBG: capillary blood glucose, VRIII: variable rate intravenous insulin infusion.

early recognition. Cerebral oedema is more common in children than in adults. Retrospective evidence suggests that pre-existing acidosis, the volume of fluid required for resuscitation, amount of insulin required and bicarbonate administration are risk factors. Pulmonary oedema is rare in DKA; the elderly and those with impaired cardiac function are at risk. It is suggested that invasive monitoring may help prevent fluid overload.

Pathway of care for the management of DKA

The JBDS guidelines split the management of DKA into four time periods :

1. The first 60 minutes
2. 60 minutes to six hours
3. Six hours to 12 hours
4. 12 hours to 24 hours

Each time period has a set of aims and actions that need to be completed in that timeframe. These aims and actions are summarised in **Table 1**.

The pathway of care also contains criteria for assessing severity of DKA. These criteria include:

- Capillary ketones over 6 mmol/L
- Bicarbonate level below 5 mmol/L
- Venous/arterial pH below 7.1
- Hypokalaemia on admission (under 3.5 mmol/L)
- Glasgow coma score less than 12 or abnormal AVPU scale
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic blood pressure (BP) below 90 mm Hg
- Pulse over 100 or below 60 bpm
- Anion gap above 16.2 mmol/L.

It is suggested that any of the above criteria, and any of the following, should warrant urgent consultant physician review and consideration for intensive care referral:

- difficulty with venous access
- failure of improvement in hypotension with basic fluid resuscitation
- high-risk patients, defined as
  - young people aged 18-25 (at higher risk of cerebral oedema)
  - elderly or pregnant patients
  - patients with heart or renal failure or any other serious co-morbidities
  - surgical patients.

General management issues

Fluid administration and deficits

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

The main aims for fluid replacement are:

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

The guidelines do suggest rates of administration to guide

Resuscitation solution	Rate (over time)	Rate (mL/hr)
0.9% saline or Hartmann's solution	1000 mL over first hour	1000 mL/hr
0.9% saline/Hartmann's solution with potassium chloride	1000 mL over next two hours	500 mL/hr
0.9% saline/Hartmann's solution with potassium chloride	1000 mL over next four hours	250 mL/hr
0.9% saline/Hartmann's solution with potassium chloride	1000 mL over next four hours	250 mL/hr
0.9% saline/Hartmann's solution with potassium chloride	1000 mL over next six hours	167 mL/hr

Regular re-assessment of fluid requirements is mandatory, and further fluid may be required.

To ensure that the fluids are actually administered, it is recommended to administer the fluids via a pump, therefore this chart includes the mL/hr rate as well.

Table 2 Initial guide to fluid resuscitation of the adult patient with DKA (Clinical assessment must define actual fluid resuscitation)

resuscitation that are shown in **Table 2**; however, clinical assessment of the patient must define actual fluid resuscitation.

Insulin therapy

A fixed-rate IV insulin infusion (FRIII) calculated on 0.1 units/kg body weight is recommended. It may be necessary to estimate the weight of the patient.

Insulin has several effects but the following are the most important when treating DKA:

- Suppression of ketogenesis
- Reduction of blood glucose
- Correction of electrolyte disturbance.

Identification of precipitating factors

The cause of the DKA must be sought and treated. The three most common triggers for diabetic ketoacidosis are:

- an underlying infection
- missed insulin treatment
- onset of previously undiagnosed diabetes (usually type 1 diabetes).

It may also be necessary to consider a surgical cause for the deterioration. If surgery is required, there needs to be an urgent, senior, multidisciplinary discussion on the optimum time to operate.

Metabolic treatment targets

The recommended targets are:

- Reduction of the blood ketone concentration by 0.5 mmol/L/hr
- Increase of the venous bicarbonate by 3.0 mmol/L/hr
- Reduction of capillary blood glucose by 3.0 mmol/L/hr
- Maintainance of potassium between 4.0 and 5.5 mmol/L

If the DKA is not improving, the FRIII rate should be increased by 1 unit/hr until the targets are met. It is also imperative to:

- reassess the patient and ensure that the precipitating cause has been identified and is being effectively treated
- check that the infusion is running and contains insulin
- ensure no artefacts are causing the aberrant results.

Conversion to subcutaneous insulin

The patient should be converted to an appropriate subcutaneous regime when biochemically stable (blood ketones less than 0.6 mmol/L, pH over 7.3) and the patient is ready and able to eat. Conversion to subcutaneous insulin is facilitated by continuation of the long-acting insulin. The transition is ideally managed by the diabetes specialist team. If the patient is either newly diagnosed and is ready for discharge to the ward, or is not tolerating an enteral diet, the intensive care team may consider establishing a variable rate IV insulin infusion (VRIII) regimen until the patient has been either commenced on subcutaneous insulin or is eating and drinking.

References for JBDS document

The guidelines are fully referenced. Due to the paucity of randomised controlled studies in this field, none of the recommendations are graded.

Conflict of interest/disclaimer

Dr Levy was a member of the 2013 writing group for the Joint British Diabetes Societies Inpatient Care Group publication 'The Management of Diabetic Ketoacidosis in Adults.'

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