Diabetic Ketoacidosis in Adults: Part 2. Management

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ABSTRACT

The priorities for the management of Diabetic Ketoacidosis (DKA) are to assess severity and establish intravenous (i.v.) 0.9% NaCl rehydration with the careful addition of potassium ($[K^+]$). Ideally, a fixed rate insulin infusion should be used initially and addition of 10% glucose infusion when the blood glucose level has fallen to below 14 mmol/l. Regular clinical and laboratory monitoring, particularly of the rate of fall of blood ketones (beta-hydroxybutyrate) and of serum $[K^+]$ and glucose is essential to guide fluid and insulin infusion rates. When the criteria for resolution of DKA are met, the patient may be switched to subcutaneous (s.c.) insulin if eating or variable rate insulin infusion if not yet able to eat and drink. Basal insulin should be continued (or started) where possible alongside infused insulin during the treatment of DKA. If fixed rate insulin infusion is not possible, then intermittent s.c. insulin injections may be used instead.

Key words: Diabetic ketoacidosis, management, insulin, potassium.

INTRODUCTION

This is the second article in a three-part series on Diabetic Ketoacidosis (DKA) in adults in this issue of the Journal. This article will focus mainly on the practical management of DKA in adults.

The advice given throughout this review is based on the Joint British Diabetes Society for Inpatient Care (JBDS-IP) guidelines for DKA[1] adapted for situations where certain medical devices or blood tests, such as infusion pumps or blood ketone measurement, may not always be readily available. Emphasis is placed throughout on pathophysiological principles so that the diagnosis and management of this condition may be optimised using whatever resources are available at the point of care.

The priorities in DKA are, in approximate order of priority:

1. To make the diagnosis and identify, and if necessary, treat the precipitant.
2. To assess the severity and resuscitate (Airway, Breathing, Circulation) as necessary.
3. To correct volume depletion and restore renal plasma flow.
4. To replace potassium (K^+).
5. To administer insulin ideally by fixed rate i.v. insulin infusion (FRII).
6. To monitor the progress of treatment.
7. To determine when DKA has resolved, institute on-going diabetes treatment and give advice to prevent recurrence.

ASSESSMENT OF SEVERITY

Severe DKA is present if any one or more of the following features are present:

- Serum beta-hydroxybutyrate > 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)
- Glasgow Coma Scale score (GCS) below 12
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic BP below 90 mmHg
- Pulse over 100 or below 60 bpm
- Anion gap above 16.

The presence of one or more of the features listed above indicates 'severe DKA'. Of these, low BP particularly when not responding to administration of a fluid bolus, severely depressed conscious level, pH<7.0 with the possibility of impending cardiovascular collapse and hypokalaemia are ominous signs requiring rapid identification and correction.

RESUSCITATION

As with any medical emergency, assessment of Airway patency, adequate Breathing and Circulation (the ABC approach) is essential. If Systolic Blood Pressure (SBP)< 90 mmHg, give 500 ml N/Saline over 10-15 min and reassess/repeat. If not responding, continue treatment and consider requesting Intensive Care assistance if available.

IV Fluids

Fluids are central in the management of DKA bearing in mind that fluid depletion is a key part of the pathogenesis. If serum potassium is <3.3 mmol/L, this should be corrected by potassium infusion before starting insulin as insulin will drive K^+ into cells thereby further, and potentially dangerously, lowering the levels. It is important to remember that insulin only inhibits new ketone formation and does not directly reduce ketone concentrations which rely on metabolism and excretion in the urine and breath. Insulin should not be commenced at the risk of provoking dangerous hypokalaemia.

Start IV fluids with 0.9% NaCl (also known as Normal Saline, N/Saline).

The aim is to expand intravascular volume, restore renal perfusion, reduce counter-regulatory hormone production and reduce secondary hyper-aldosteronism. Excretion of ketones and glucose will increase as a result of volume correction.

A typical fluid deficit is of the order of 100ml/kg (10%) in severe DKA and a typical regime for replacement is shown in the table below.

0.9% Saline Administration Regime for Adults in DKA

Consider the need for one or more fluid boluses if SBP<90 mmHg (see 'Resuscitation' above). Following this, or if bolus not considered necessary, infuse:

- 1L 0.9% Saline over 1h i.v.
- 1L 0.9% Saline over 2h i.v.
- 1L 0.9% Saline over 2h i.v.
- 1L 0.9% Saline over 4h i.v.
- 1L 0.9% Saline over 4h i.v.
- 1L 0.9% Saline over 6h i.v.
- Note: K+ replacement is essential and see below for details.

Take a more cautious approach in the elderly, those with heart or renal failure, in pregnancy and in young people due to the increased risk of cerebral oedema. Consider the need for infusing glucose (5%, 10% or more concentrated depending on circumstances and availability) at the same time if blood glucose levels are not sufficient to permit adequate insulin infusion without hypoglycaemia (see 'Fixed Rate Insulin Infusion' below).

Potassium replacement

Most DKA patients will be K^+ depleted. A further drop in [K^+] may be anticipated with insulin infusion. Do not initiate insulin if potassium is <3.3mmol/l to prevent cardiac dysrhythmias and respiratory muscle weakness. Replace potassium intravenously and in general do not exceed a rate of 20 mmol/h by peripheral infusion (higher concentrations and rates may be given under Intensive Care type monitoring via a central line). Be prepared to adapt this regimen in patients with established renal failure and exercise great caution in potassium infusion until it is clear that there is a good urine output. Aim to maintain serum potassium levels between 4 and 5 mmol/l.[2]

Serum [K^+]	Amount of K^+ to add to each litre of 0.9% Saline
>5.5	Nil
3.5-5.5	20-40 mmol depending on [K^+] and fluid infusion rate
< 3.5	Seek senior advice, consider infusion via central venous catheter, do not start insulin until above 3.3 mmol/l

Fixed Rate Insulin Infusion (FRII)

- Add 50 Units of human soluble insulin (e.g., Actrapid, Humulin S) to 50 ml 0.9% NaCl in an infusion pump and start the fixed rate insulin infusion at 0.1 unit/kg/h. For example, in a 70 kg individual this gives 7 units insulin/hour (7 mls of this infusate per hour).
- If hourly blood ketones are not dropping based on target rates of decline (≥0.5 mmol/L/h), then increase insulin infusion rate by 1 unit/h and reassess after one hour.
- Where blood ketone measurements are not easily available, use venous [HCO_3^-] instead (target rise is ≥3.0 mmol/L/h). Plasma glucose can be used as a last resort (target fall is ≥3.0 mmol/L/h) although this is not reflective of the resolution of acidosis.

In the past, DKA was often treated using 'Variable Rate Insulin Infusions' (VRII, sometimes known as 'sliding scale insulin infusions'). These vary the number of units of insulin infused per hour according to the prevailing blood glucose levels and will usually result in successful treatment eventually. However, this approach has now widely been superseded by the 'Fixed Rate Insulin Infusion' in which a constant, weight-based dose of insulin is infused hourly and if necessary, glucose is infused at the same time alongside 0.9% Saline to prevent hypoglycaemia.

The drawback of VRII is that as the levels of blood glucose fall (mostly through expansion of the extracellular fluid compartment, glucose losses in the urine and increased glucose uptake, metabolism and storage in insulin sensitive tissues), the rate of insulin infusion may be decreased to a level that is no longer sufficient to suppress ketogenesis. In other words, adjusting insulin infusion based on glucose level and using it as a marker will lead to reduction of infused insulin whilst the patient is still in ketoacidosis and may prolong the duration of the ketoacidotic state.

By infusing a weight-based hourly amount of insulin that is known to suppress ketogenesis, even in the insulin resistant conditions of DKA, a more rapid correction of DKA is achieved. VRII can give the misleading impression that the target for correction in DKA is the blood glucose level when in fact, it is the volume and potassium depletion, acidosis and ketone accumulation that form the therapeutic goals. The main disadvantage of FRII is the risk of developing hypoglycaemia, hence the need to co-infuse glucose as blood glucose levels fall.

In addition to the FRII, the patient's usual long-acting basal insulin should be continued from the outset (e.g., Degludec (Tresiba), Glargine (Lantus/Toujeo), Detemir (Levemir) or Human Isophane Insulin (Humulin I, Insulatard). In a newly diagnosed patient with type 1 diabetes not previously on a basal insulin, basal insulin may be given s.c. once daily at a dose of 0.25 Units/Kg. (e.g., for a 70 kg individual = 18 units). This ensures the presence of insulin in case of interruption in the insulin infusion and allows a smooth transition to the usual subcutaneous insulin regimen of the patient when he or she is able to eat and drink after ketoacidosis has resolved. Early administration of long-acting insulin glargine has shown to protect from rebound hyperglycaemia[3] without increasing the risk of hypoglycaemia and the average time required for recovery is reduced.[4]

The JBDS-IP guidelines recommend considering reduction of the Fixed Rate Insulin Infusion to 0.05 U/kg/hour once glucose is <14 mmol/l.

- 10% Glucose (or equivalent) must be infused (typically starting at a rate of 125 mls/h and titrating to response) when the blood glucose level falls to below 14 mmol/l to prevent hypoglycaemia until the conditions for resolution of DKA are met (see below) and the FRII is stopped.
- Once resolution criteria are met, variable rate insulin infusions (together with infusion of 5% Glucose and K^+) may then be administered unless or until the patient is able to eat and drink and resume (or start, if newly diagnosed) subcutaneous insulin treatment.

Monitoring intervals

Monitoring intervals will depend on initial severity of the DKA, progress in response to treatment and available resources. However, as a guide, the following are useful starting points.

- Capillary glucose and ketones: Hourly until resolution
- Venous blood gas (HCO_3^- & K^+): 2h, 4h, 8h, 12h and 24h
- Plasma electrolytes: Every 4 hours until resolution

In addition to this, close monitoring of conscious level, clinical improvement and fluid sufficiency (especially recommended at 12 hours) should be carried out.

Criteria for resolution of DKA and transfer to subcutaneous insulin

By 24 hours DKA should have resolved in the majority of patients- in practice, many will have fully recovered within 6-12 hours of optimal treatment. Criteria for resolution of DKA and transfer to VRII (if still unable to eat and drink) or s.c. insulin (if eating and drinking) are as set out below.

Criteria for resolution of DKA

- Blood ketones <0.6 mmol/l AND
- Venous pH >7.3
- (Venous HCO_3^->15 mmol/l can be used but may be

delayed by hyper-chloraemic acidosis after the DKA has in fact fully resolved- see 'pitfalls' in Part 3 of this series.[5]

If the patient is eating and drinking, transfer to subcutaneous insulin given with food. Give the fast-acting insulin (e.g., Humulin S, Actrapid, Novorapid, Humalog, Apidra) with a meal and stop the i.v. insulin infusion 30-60 minutes thereafter to allow some time for the subcutaneous insulin to be absorbed.

If the patient was not previously known to have diabetes, a reasonable starting point for s.c. insulin is to give 0.4-0.5 units/kg/day of insulin in total, half of which long acting and half of which rapid acting insulin, the latter half shared between 3 meal time doses. For example, in a 70 kg individual, 14-18 units of long acting or 'basal' insulin once daily together with 5-6 units of rapid acting insulin with each meal.

These doses are only starting points and would be titrated to blood glucose readings in the fasting (for basal insulin) or 2-hour post-prandial (for soluble or rapid acting insulin) states bearing in mind that patients are usually insulin resistant when recovering from ketoacidosis so doses should be conservative to allow for this. It is important to avoid a hypoglycaemic episode shortly after starting insulin which may reduce their confidence in both insulin treatment and also in the prescribing physician.

If the patient has met the criteria for DKA resolution but is not yet eating and drinking, transfer to variable rate insulin infusion (VRII) until such time as they are.

SUMMARY

The priorities in DKA management following diagnosis are to assess severity, consider the need for involvement of critical care physicians if available and establish i.v. 0.9% NaCl rehydration with the addition of K^+ as described.

Ideally, a fixed rate insulin infusion should be used initially with consideration of insulin dose reduction (halving) and addition of 10% Glucose infusion when the blood glucose level has fallen to below 14 mmol/l. Regular clinical and laboratory monitoring, particularly of the rate of fall of blood ketones (hydroxybutyrate) and of serum [K^+] and glucose is essential to guide fluid and insulin infusion rates.

Once the criteria for resolution of DKA are met, the patient may be switched to s.c. insulin if eating or variable rate insulin infusion if not yet able to eat and drink.

Basal insulin should be continued (or started) where possible alongside infused insulin during the treatment of DKA.

Where facilities are not available for fixed rate insulin infusion, intermittent s.c. insulin injections may be used instead. Suitable regimes are described together with a number of pitfalls and special situations in DKA management in the third and final part of this series.[5] The first paper in this series is on Pathogenesis and Diagnosis.[6]

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