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# Diabetic Ketoacidosis: A Review of Risk Associated Morbidity and Mortality

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## Abstract

Diabetic ketoacidosis (DKA) is a rare yet potentially fatal hyperglycemic crisis that can occur in patients with both type 1 and 2 diabetes mellitus. Due to its increasing incidence and economic impact related to the treatment and associated morbidity, effective management and prevention is key. Elements of management include making the appropriate diagnosis using current laboratory tools and clinical criteria and coordinating fluid resuscitation, insulin therapy, and electrolyte replacement through feedback obtained from timely patient monitoring and knowledge of resolution criteria. In addition, awareness of special populations such as patients with renal disease presenting with DKA is important. During the DKA therapy, complications may arise and appropriate strategies to prevent these complications are required. DKA prevention strategies including patient and provider education are important.

## Keywords

Diabetic Ketoacidosis, Diabetes, Insulin, Rehydration, Hypoglycemia, Hypokalemia, Metabolic Acidosis, Protocol.

## Introduction

Diabetic ketoacidosis (DKA) is characterised by the triad of hyperglycemia, ketosis, and metabolic acidosis. This results from a relative or absolute deficiency of insulin and an excess of counter-regulatory hormones including glucagon, cortisol, catecholamines, and growth hormones leading to hyperglycemia, glycosuria, dehydration, and hyperosmolarity of varying severity. lycosuria induces an osmotic diuresis, which results in significant deficits in fluid and electrolytes including sodium, potassium, calcium, magnesium, chloride, and phosphate [3]. Dehydration and hyperglycemia results in hypertonicity and an efflux of water from the intracellular space to the hypertonic extracellular space. There is also a potassium efflux from the intracellular space, aggravated by acidosis, lack of effective insulin action, and breakdown of intracellular proteins [3].

Diabetic ketoacidosis more often complicates type 1 rather than type 2 diabetes mellitus and carries the risk of significant morbidity and mortality [1, 4, 5]. Despite evolving practice, there are increasing numbers of hospital admissions for DKA and hyperosmolar hyperglycaemic state (HHS) [1, 6, 7]. DKA is associated with mortality rates as high as 5–9% in the elderly and in patients with severe comorbidities [1, 8]. DKA itself is a hypercoagulable state resulting in potentially fatal complications including stroke, myocardial infarction, and disseminated intravascular coagulation [9, 10]. Management involves rehydration, correction of electrolyte derangements; particularly hypokalaemia, administration of insulin, correction of metabolic acidosis, and treatment of precipitants such as infection, pancreatitis, trauma, and myocardial infarction [11–13].

## Aims of Review

This review is intended to assist those writing and utilising DKA management protocols in adults to appreciate deficits in current knowledge and to draw attention to areas that may benefit from future research.

We reviewed the original studies considering key elements of inpatient management of DKA including the choice of intravenous fluids and rates of replacement; insulin infusion rates, and routes of administration; potassium replacement rates; and the role of bicarbonate and phosphate replacement.

## Methods

### Hydration

Patients with DKA experience osmotic diuresis, resulting in hyperosmolar intracellular dehydration [14]. Fluid deficits may be up to 10% of total body weight [1, 5]. There is also an accumulation of β-hydroxybutyrate and acetoacetate, which results in a high anion gap metabolic acidosis [1]. Prompt rehydration is vital to restore circulating volume and tissue perfusion, clear ketones, and correct electrolyte imbalances [1, 5, 14]. Independent of insulin therapy, hydration alone restores circulatory volume and tissue perfusion; improves glycaemic control and acid base balance, and reduces counterregulatory hormones.

However, specifically hydroxyethyl starch crystalloids were associated with a significant increase in mortality and acute kidney injury, and it was concluded that they should be avoided [14–19]. It is important to note that none of the included studies specifically considered these fluids in the setting of DKA.

During the recovery phase of DKA, hyperchloraemia tends to develop because of preferential excretion of ketones during rehydration and improved renal perfusion, resulting in a raised anion gap metabolic acidosis [14]. It is proposed that rehydration with normal saline may contribute to hyperchloraemia and a hyperchloraemic metabolic acidosis with a persisting base deficit and may cause renal vasoconstriction and decreased glomerular filtration rate [14, 27]. Alternatively, this acidosis may represent a physiological response to resolving DKA rather than a result of the hydration fluid itself [17, 20–23, 28].

The only other RCT was also small, studied different crystalloids in DKA, comparing patients who received Ringer's lactate (a balanced electrolyte solution) ($n = 28$) with patients who received normal saline ($n = 29$). In this study, Ringer's lactate offered no significant superiority in time to normalisation of pH and took a significantly longer time to achieve a blood glucose concentration ≤14mmol/L [26]. A proposed mechanism for this delay in control of blood glucose level was that lactate from Ringer's solution provided excess substrate for ongoing gluconeogenesis [26]. Using the 2006 (and then the 2009 *post hoc*) American Diabetes Association (ADA) definitions for resolution of DKA, fluid selection made no statistically significant difference in time to resolution [26].

## Potassium Replacement—Dose and Rates

Patients with DKA are often found to initially have mild to moderate hyperkalaemia, despite a total body deficit of potassium [1]. The initiation of insulin causes an intracellular shift of potassium and lowers the potassium concentration potentially resulting in severe hypokalaemia. Hence patients with serum potassium levels <3.3mmol/L need initial management with fluid resuscitation and potassium replacement, whilst delaying commencement of insulin until after potassium levels are above 3.3 mmol/L, to avoid cardiac arrhythmias, arrest, and respiratory muscle weakness [2].

## Insulin Administration

Once hypokalaemia is corrected and hydration commenced, insulin should be administered to halt lipolysis, ketogenesis, and correct hyperglycaemia. Regular insulin is favoured over insulin analogues. The current mainstay of insulin therapy in DKA is continuous intravenous infusion for its rapid onset and ease of dose titration [1, 2]. Some institutions require intravenous insulin infusions to be managed in the intensive care setting and thus some advocate for the use of subcutaneous or intramuscular injections in order to avoid an intensive care admission [1, 46–48].

## Insulin—Role of Initial Intravenous Insulin Bolus

An initial intravenous insulin bolus has been considered in multiple small trials.

A small prospective analysis in 1995 found patients who received an insulin bolus had a significantly higher incidence of hypoglycemia but no difference in hypokalaemia [57].

In contrast, a prospective observational cohort study in 2007 ($n = 157$) found no statistical difference in the incidence of hypoglycaemia, rate of glucose reduction, or length of hospital stay [63] and concluded that an initial bolus of intravenous insulin offered no significant clinical benefit or harm. The study was limited by lack of randomisation; standardised treatment protocols and used administration of 50% dextrose as a surrogate definition for hypoglycemia rather than serum glucose levels.

In 2008, a small prospective randomised protocol established that an initial bolus of insulin avoided the need for supplemental insulin doses if the insulin infusion rate was less than 0.14 units/kg/h [1, 64]. The study compared patients ($n = 12$) who received a loading dose of 0.07 units/kg of regular insulin, followed by 0.07 units/kg/h insulin infusion, group 2 ($n = 12$) insulin infusion at 0.07 units/kg/h without loading insulin and group 3 ($n = 13$) insulin infusion at 0.14 units/kg/h, without loading. It found that group 2 patients required supplemental insulin doses, whilst other patients did not. Otherwise, there was no significant difference in duration taken to reach a serum resolution of DKA, length of hospital stay, hypokalaemia, or other complications including death [64].

## Glucose Infusion

Glucose infusion is recommended when blood glucose levels falls below 10–14 mmol/L [1, 5, 29, 68] to avoid hypoglycaemia [3, 5] and to reduce the development of ketosis [3, 5, 29]. However, the choice of these thresholds is somewhat arbitrary.

Regarding the choice of fluid for maintenance of adequate glycaemic control, 5% dextrose was compared to 10% dextrose in a small RCT ($n = 17$). This study found that 10% dextrose resulted in significantly lower level of ketonaemia and a higher level of hyperglycaemia but did not result in any benefits in correction of acidosis or bicarbonate levels [36].

## Interpretation of DKA Correction Rate

Studies have traditionally used time to correction of DKA as a surrogate end point for patient outcomes, where resolution of DKA is defined as BGL < 11mmol/L and two of the following criteria: serum bicarbonate level ≥15 mmol/L, venous pH >7.3 and a calculated anion gap ≤12 mmol/L [2]. Despite the assumption that faster correction of DKA leads to better outcomes with shorter intensive care and hospital admission, there have been no studies which specifically establish this relationship.

A prospective trial ($n = 114$) concluded that very low-dose insulin administration and slow re-equilibration were the fundamental strategies in optimal management [69]. The study used a basal insulin infusion of 1 unit/h, with a maximal decrease of blood glucose level of 3 mmol/L/h, reaching a mean blood glucose of 14 mmol/L at 12 h, whilst rehydrating with 1 L/h for the first 4 h. This approach resulted in no mortality or lasting deficiencies in a small cohort [69].

## Results

Regarding protocol impact on DKA treatment outcomes, a retrospective study compared patients managed with and without local protocol, found that patients treated with a local protocol had a significantly shorter mean time to normalisation of serum bicarbonate, lower incidences of hypokalaemia, and lower incidence of hypoglycaemia, and no significant difference in total insulin dose

## Bicarbonate

Significant controversy surrounds the role of bicarbonate replacement in DKA. Some argue that correcting ketosis with insulin is adequate for reversing acidosis Others argue that bicarbonate therapy is warranted given the complications of severe metabolic acidosis.

## Impact of insulin administration routes on diabetic ketoacidosis

| Insulin types | Outcomes measured | Effect size | Number of participants and trials |
| --- | --- | --- | --- |
| SC insulin lispro vs. IV regular insulin | Mean difference in time to resolution of DKA | 0.2 h (95% CI −1.7 to 2.1) ($p = 0.81$) | ($n = 90$, 2 trials) |
| SC insulin aspart vs. IV regular insulin | Mean difference in time to resolution of DKA | −1 h (95% CI −3.2 to 1.2) ($p = 0.36$) | ($n = 30$, 1 trial) |
| SC insulin lispro vs. IV regular insulin | Hypoglycemic events | Ratio of 0.59 (95% CI 0.23–1.52) ($p = 0.28$) | ($n = 156$, 4 trials) |
| SC insulin aspart vs. IV regular insulin | Risk of hypoglycaemic episodes | Risk ratio 1.00 (95% CI 0.07–14.55) ($p = 1.0$) | ($n = 30$, single trial) |
| Insulin lispro vs. IV regular insulin | Difference in mean hospital length of stay | −0.4 days (95% CI −1 to 0.2) ($p = 0.22$) | ($n = 90$, 2 trials) |
| SC insulin aspart vs. IV regular insulin | Difference in mean length of stay | 1.1 days (95% CI −3.3 to 1.1) ($p = 0.32$) | ($n = 30$, single trial) |

## Discussion and Conclusion

On review, the strength and breadth of original evidence is limited. Current weak evidence suggests crystalloids are preferred over colloids. There is no clear evidence for superiority of a given crystalloid nor for a given rate of rehydration.

Low-dose insulin has limited evidence for superior safety over high-dose insulin. Administering bolus insulin prior to low-dose insulin infusions <0.14 units/kg/h may obviate the need for additional insulin supplementation. Intravenous regular insulin infusions are traditionally preferred, with emerging evidence for non-inferiority of subcutaneous insulin and with no head to head comparisons between fixed weight-based versus blood glucose-based insulin dosing regimens. Clear evidence is lacking for timing of initiation and titration of dextrose infusions, in addition to replacement of potassium, phosphate, bicarbonate.

Traditionally, studies have used mean time to resolution of DKA as favourable end points, although this correlation has no supporting evidence.

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