

# The evolution of DKA management

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## Abstract

**The Joint British Diabetes Societies (JBDS) looked in detail at the evidence based management for diabetic ketoacidosis (DKA) and generated a set of guidelines to support the management of this complex condition. Because of the nature of research into DKA there are some areas which have less of an evidence base, so expert commentary and experience support several of the recommendations. This article describes the historical basis of the development of the management of this condition, how we came to arrive at the present situation and why the ongoing national DKA audit is so important in elucidating what is currently happening across the UK in clinical practice.**

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**Key words:** diabetic ketoacidosis, guideline development, diabetic coma, insulin, evidence based medicine.

## Introduction

In 2010 the JBDS produced a national guideline for the management of DKA.<sup>1</sup> By 2013 data presented at the Diabetes UK Annual Professional Conference showed that over 85% of all UK hospitals who responded to an online questionnaire said that they had either adopted or adapted the guideline. In 2013 the guideline was then updated to reflect new evidence and to incorporate some of the suggestions, criticisms and comments made about the first edition.<sup>2</sup> However, there remain some concerns about the document; most frequently aired are those surrounding the lack of evidence for many of the recommendations. For this reason the current national audit on the management of DKA is taking place – to try to gather information about what is currently being done, and whether the current guideline helps or hinders management, or if there are areas that need to change to improve outcomes. I hope that by the time you read this your team will have contributed to the audit by submitting data on five patients admitted to your hospital with DKA, as well as the institutional form that is gathering information about the make-up of diabetes teams across the UK.

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## Abbreviations and acronyms

ABCD	Association of British Clinical Diabetologists
DKA	diabetic ketoacidosis
FRIII	fixed rate intravenous insulin infusion
JBDS	Joint British Diabetes Societies

The data are being collected from all adult teams as well as for all DKA admissions for those aged over 14 years from paediatric teams. If you are based in a UK hospital and still want to submit data, then please do so by downloading the forms from the ABCD website at <http://www.diabetologists-abcd.org.uk/Lists/Announcements/AllItems.htm>.

One of the most frequent questions to arise is ‘why?’. Why does the guideline recommend a weight based, fixed rate intravenous insulin infusion when for years it was a variable rate; why the move to bedside ketone measurements; why venous blood gases; and so on. To answer these, and many other questions, it may be useful to look at the history of DKA and its management.

## The pre-insulin era

One of the earliest descriptions of ‘the diabetic coma’ was from 1886.<sup>3</sup> In it, the author describes how, for those unfortunate individuals who developed type 1 diabetes, life was miserable, and usually very short. It had previously been recognised that fasting (or rather, enforced rationing) had relieved the glycosuria of diabetes during the German siege of Paris in 1870 and this led to the development of severe, carbohydrate-free diets. By the turn of the century several eminent diabetes specialists such as Fredrick Allen in the USA, or Bernard Naunyn in Germany, managed to keep people alive for a few months, or even a year or two on these strict, unpalatable regimens.<sup>4</sup>

The introduction of insulin in 1922–23 was possibly the greatest medical breakthrough of the 20th century. What dogged those who were ‘early adopters’ of the new wonder drug was how to use it – how often, how much, and so on, and how to balance the glucose lowering effects with the risks of going too low or not administering enough to prevent ketosis. It was on this background that the management of DKA evolved.

## High dose insulin

An early report on the management of DKA during the first 20 years after the availability of insulin documented that between January 1923 and August 1940 12% of patients died if they presented with DKA, and they were given, on average, 237 units

of insulin in the first 24 hours – with a mean of 83 units being given in the first 3 hours.<sup>5</sup> The author went on to report that between August 1940 and May 1944, only 1.6% of patients died, and the average insulin dose given in the first 24 hours was 287 units (range 50 to 1770 units), with a mean of 216 units being given in the first 3 hours.<sup>5</sup> Thus, high-dose insulin treatment for the management of DKA became the ‘norm’. In 1949, Black and Malins from Birmingham reported a case series of 170 consecutive cases of DKA treated with an average of 265 units (range 140 to 500 units) of intravenous insulin for those who were drowsy but rousable, an average of 726 units (range 250 to 1400 units) for those who were rousable with difficulty, and an average of 870 units (range 500 to 1400 units) for those who were unconscious on admission.<sup>6</sup> What was lacking, of course, in those very early reports was aggressive fluid management. Black and Malins reported that they would usually give ‘a pint [568 mL] of saline over 15–30 minutes, followed by a second pint given administered at the same rate, and then perhaps a third, followed by 5% glucose given at a pint per hour’.<sup>6</sup> They were, however, also amongst the first to describe a classification of severity for DKA, something that the American Diabetes Association continues to advocate.<sup>7</sup>

#### Low dose insulin and aggressive fluid replacement

Whilst there had been sporadic reports of low dose insulin being used to successfully treat DKA, it was not until Sönksen *et al* in 1972,<sup>8</sup> and subsequently Kidson *et al*<sup>9</sup> and Page *et al*<sup>10</sup> in back-to-back publications in the *British Medical Journal*, who showed that low dose insulin infusions given intravenously, adequately lowered ketone and glucose levels. The doses used were 1.2 to 9.6 units per hour from Kidson *et al*, and a fixed rate of 6 units per hour from Page *et al*. In addition, the 6 units per hour that Kidson *et al* administered resulted in a plasma insulin concentration of ~100  $\mu\text{U/mL}$ . This was compared with a concentration in a healthy individual of ~40–50  $\mu\text{U/mL}$  [ $<20$  fasting,  $>40$  prandial].<sup>9</sup> The weight based FRIII has also now been used successfully for several decades.<sup>7,11</sup> The concept of an FRIII is well established in paediatric diabetes,<sup>12</sup> and the question often arises ‘when does a child become an adult?’.

What was still missing from the report by Kidson *et al* was the fluid replacement regimen. Page *et al* comment that they gave 3.66L (range 1.5 to 6 L) in the first six hours, and a mean of 5.5L (range 2.75 to 9 L) in the first 12 hours. Thus an aggressive fluid regimen given together with a low dose intravenous insulin infusion regimen became the standard of care for the management of DKA for the next four decades.

#### The diabetes specialist team

In the UK over the last 30 years diabetes has developed into a medical speciality in its own right. Many of the people who were appointed in the 1970s and 1980s as ‘general physicians with an interest in diabetes’ have now been overtaken by ‘consultants in diabetes and general medicine’. This shift, whilst apparently minor, has had implications for the management of patients with diabetes in general, but in particular for those presenting with

DKA. It was demonstrated in the late 1990s that, when patients with DKA were looked after by doctors specialising in diabetes, their outcomes were better than patients treated by ‘general physicians’.<sup>13</sup> With the advent of the Diabetes Inpatient Specialist Nurse,<sup>14</sup> there has been a wholesale move towards diabetes care being delivered by the specialist diabetes team. Indeed, with the recent implementation of the Best Practice Tariff for DKA, there is now a financial incentive for hospitals to provide such a service.<sup>15</sup>

#### Ketone and venous blood gas measurement

In 1972 Hockaday and Alberti suggested that a plasma ketone body concentration of greater than 3 mmol/L would equate to ‘severe’ acidosis.<sup>16</sup> However, the technology needed to measure ketones was not routinely available. The development of urine ketone monitoring was a major advance, and became the recommended standard of care when monitoring the treatment of DKA.<sup>17</sup> As the physiology of ketosis became better understood, it became apparent that, whilst urine ketone sticks detected aceto-acetic acid, they were poor at detecting  $\beta$ -hydroxybutyrate, the predominant ketone in the blood. With the advent of hand-held bedside ketone monitoring equipment there came a better understanding that the pathological problem in DKA is the ketosis/acidosis rather than the hyperglycaemia.<sup>18</sup>

The avoidance of arterial blood gases is to be welcomed. This author vividly recalls a radial artery aneurysm caused by an arterial blood gas sample rupturing on my last night on call as a medical registrar (treated with the judicious use of a sphygmomanometer). Evidence has shown that the difference between arterial and venous pH and bicarbonate is not large enough to alter management and is far less invasive for the patient.<sup>19</sup>

#### Where are we now?

By the late 1990s and early 2000s there was a consensus that the best way to treat DKA was with aggressive fluid management and a low dose intravenous insulin infusion. In addition, it was agreed that regular monitoring of blood gases aided management decisions. It was also recognised that electrolyte deficiencies were common and that for some – potassium in particular – replacement was necessary. What there was no consensus about, however, was how much fluid, which fluid, how much insulin, venous or arterial gases, how much potassium, bicarbonate yes or no, phosphate yes or no, and so on. Thus it was often left to individual hospitals to come up with their own DKA guideline (and for the incoming registrar to rewrite it!). It was in 2006 that the ABCD asked two leading clinicians to construct a set of guidelines that would form the basis of a standardised treatment regimen.<sup>20</sup> It quickly became clear that there was an appetite for such a document for use by those at the ‘front door’. However, it needed to be more detailed and more evidence based for emergency teams to accept its use. It was at this time that the JBDS Inpatient Care Group was also formed: a collaboration between ABCD, Diabetes UK, and the National Diabetes Inpatient Nurse Group comprising individuals interested in inpatient care. The authors of the initial ABCD DKA guideline



## Key messages

- DKA is a medical emergency which continues to have an associated morbidity and mortality
- The modern management of DKA consists of aggressive fluid replacement and a fixed rate insulin infusion determined by body weight, followed by regular monitoring of metabolic markers along with supportive care based on the level of severity
- The JBDS DKA guidance is dynamic: the new numbers needed to treat to answer questions about the 'nuances' are enormous and randomised controlled trials are therefore unlikely to be done
- The optimal treatment strategy has yet to be determined

were joined by others and a more comprehensive document was written,<sup>1</sup> and revised in 2013.<sup>2</sup> Given the infrequency and heterogeneity of the condition, it remains difficult for any one team to see sufficient numbers of cases to be able to assess the impact of the guidelines. For this reason, there is currently an audit of DKA management – based loosely on the JBDS guideline. It is designed to capture data on five consecutive admissions with DKA at all hospitals across the UK and to see if and where the management of DKA could be improved. The same audit form is also being used to assess the care of all paediatric patients aged over 14 years.

### Future directions

The optimal treatment for DKA has yet to be determined. The numbers needed to treat to answer questions about the 'nuances' would be enormous and randomised controlled trials are therefore unlikely to be done. Until then, consensus and audit have to suffice. As with all JBDS documents, the DKA guideline is dynamic. If the current audit shows the need for changes, then they will be made. In the meantime, please contribute to the audit, and if you have criticisms, comments, or suggestions feel free to air them.

**Conflict of interest** KD was the lead author on the 2nd edition of the JBDS guideline on the management of DKA in adults referred to in the text. Travel to meetings for the writing group during production of the guideline was paid for by Diabetes UK

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