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ORIGINAL ARTICLE

Heterogeneity in the management of diabetic ketoacidosis in Australia: a national survey

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Abstract

Background: Diabetic ketoacidosis (DKA) is a hyperglycaemic emergency, and insulin administration is highly protocolised with either variable- or fixed-rate intravenous infusions. There are limited data supporting superiority of one regimen over another; however, international guidelines recommend fixed-rate infusions.
Aim: To characterise DKA management protocols used in Australian hospitals.
Methods: An online survey of Australian endocrinologists and intensive care physicians between May and July 2024. The main outcome measure was the proportion of respondents using a fixed or variable rate, or combination, for the management of DKA. Secondary outcomes were the location of management, definition of resolution and intravenous fluid specification.
Results: There were 31 respondents from individual hospitals around Australia, with 84% of endocrinologists and 84% from metropolitan hospitals. There was wide variation in insulin regimens including fixed ($n = 12$), variable ($n = 14$) and combination ($n = 5$) infusion protocols. Most (23/30, 77%) respondents had worked at another hospital that had a different DKA management protocol. There was a 50% split ($n = 14$ each) in personal preference for fixed- or variable-rate infusion, with three respondents having no preference. Most (21/31, 68%) protocols defined resolution of DKA. Blood pH (15/21, 71%) and/or ketone level (18/21, 86%) were the most frequently used end points to define resolution.
Conclusions: There are substantial variations in insulin regimens and resolution criteria in DKA management protocols across Australian hospitals. Clinician preference was diverse. This likely reflects the lack of high-quality evidence to guide practice.

Introduction

Diabetic ketoacidosis (DKA) is a potentially life-threatening emergency resulting from insufficient insulin. The treatment for DKA involves exogenous insulin administration, hydration, electrolyte replacement and treatment of the underlying precipitant. Intravenous insulin is generally the standard of care for treatment of DKA.[1,2] Intravenous insulin can either be infused at a variable rate, where the rate of the insulin infusion is titrated based on the glucose concentration, or at a fixed rate, where the insulin infusion rate is constant and often based on bodyweight. The management of DKA has become highly protocolised to allow rapid commencement of treatment by emergency physicians and then continuation of therapy, either in intensive care or on medical wards.

Use of variable-rate insulin infusions is based on the premise that ketosis and hyperglycaemia are linked; administering higher doses of insulin when glucose concentration is high may allow greater suppression of ketosis and result in faster reduction in plasma ketones. Conversely, when the

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glucose concentration is lower, ketone concentration is likely also lower and less insulin will be administered, which will also protect against hypoglycaemia. Fixed-rate insulin infusions would be expected to deliver a greater amount of insulin overall and have been recommended on the assumption that a threshold of plasma insulin concentration is required to suppress ketosis. There is limited evidence about how each of these insulin infusion protocols affects patient outcomes. Retrospective studies have implied that time to resolution of DKA is similar between fixed and variable insulin regimens.[3–5] However, some studies have suggested increased rates of hypoglycaemia with fixed-rate insulin infusions.[3,4] Despite this, many international guidelines recommend fixed-rate insulin infusions.[1,2,6] There are a paucity of data on the Australian experience of DKA management, although anecdotally it has been suggested that there is marked heterogeneity in management protocols and the site of treatment (intensive care unit (ICU), high dependency unit or medical ward) between hospitals. Intravenous insulin infusions are labour intensive, requiring frequent biochemical and clinical monitoring due to the rapid shifts in electrolytes and blood glucose.

The decision of when to transition patients from intravenous insulin to subcutaneous insulin and the choice of resuscitation fluid also remains controversial. The former relates to concern that early transition will result in re-bound ketosis and the latter stems from the possibility that hyperchloremia could contribute to acidosis with infusions of 0.9% sodium chloride, although the relative importance compared to ketone-driven acidosis is not clear.[7]

In recent years, the frequency of sodium glucose co-transporter inhibitor (SGLT2i)-associated DKA has increased.[8,9] In this setting, variable-rate infusions have been associated with both prolonged time to resolution and hypoglycaemia.[10] It is unclear whether protocols address the different management requirements of DKA based on aetiology.

In light of these substantial areas of variation, we assessed the variation in DKA management across Australia.

Methods

We undertook an observational study in the form of a structured online survey using a REDCap electronic data capture tool hosted by St Vincent's Hospital, Sydney.[11,12] Email invitations were sent out via the Endocrine Society of Australia (ESA) mailout and an intensive care special interest group. The survey was included in one ESA eBulletin (5 June 2024) and in one ESA rural group email (27 June 2024). The intensive care special interest group email (2 July 2024) included 42 Australian intensivists. The invitation email set out the rationale of the survey and indicated the estimated time taken to complete the survey of 5–10 min. Participation in the survey was voluntary and required prospective consent. The survey was open from the 1st of June until the 22nd of July 2024.

Survey

Our survey (Data S1) included quantitative and open text questions about DKA protocols used at the participant's hospital. The survey was tested by the authors on their own devices.

Outcome measures

The primary outcome was the proportion of respondents using a variable-rate insulin infusion protocol.

Key secondary outcomes were a description of the definition of DKA resolution, specification of intravenous fluid use, continuation of subcutaneous insulin and location of DKA management within the hospital.

Definitions

Type of insulin infusion was offered as selection of either (i) 'fixed insulin rate, for example, based on weight', (ii) 'variable insulin rate, for example, based on glucose level and changes as the glucose level changes' or (iii) 'combination'. 'Combination' was used to allow for hospitals that used aspects of both fixed and variable insulin infusion protocols.

The primary location of management of DKA was offered as a single selection of either (i) emergency department, (ii) ICU, (iii) high dependency unit, (iv) ward or (v) other.

Statistical analysis

Summary statistics for categorical measures include sample size, frequency and percentages. For continuous measures, summary statistics include sample size, mean and standard deviation or median and interquartile range. Qualitative responses were categorised.

Ethics approval

Ethics approval was provided by the Human Research and Ethics Committee, St Vincent's Hospital Sydney (2024/ETH00868).

Results

Type of intravenous insulin infusion

There were 31 responses from individuals working at 31 hospitals around Australia, including public and

Table 1 Baseline characteristics of the survey based on type of insulin infusion used for management of DKA

	Fixed ($n = 12$)	Variable ($n = 14$)	Combination ($n = 5$)
State/territory			
ACT	1	0	0
NSW	4	5	1
NT	0	0	2
QLD	3	1	0
SA	0	5	0
Tas	0	0	0
Vic	0	3	2
WA	4	0	0
Geographic type			
Metropolitan	10	13	3
Regional	2	1	1
Remote	0	0	1
Type of hospital			
Public	11	13	5
Private	1	1	0
Patient population			
Adults	10	14	5
Paediatrics	1	0	0
Both	1	0	0

ACT, Australian Capital Territory; DKA, diabetic ketoacidosis; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; Tas, Tasmania; Vic, Victoria; WA, Western Australia.

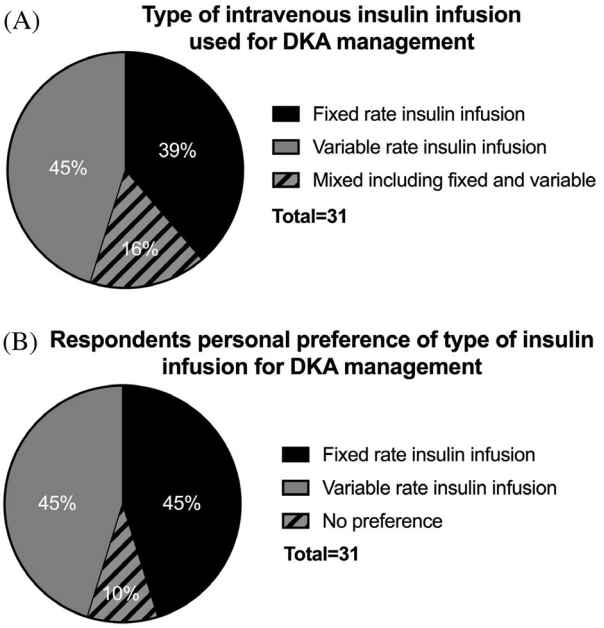

Figure 1 (A) Responses for type of intravenous insulin infusion used for diabetic ketoacidosis (DKA) management. (B) Respondents personal preference of type of insulin infusion for DKA management.

private hospitals, and city and regional locations (Table 1). The majority ($n = 26$, 84%) of respondents were endocrinologists. There was a mix of fixed ($n = 12$, 39%), variable ($n = 14$, 45%) and combination ($n = 5$, 16%) insulin infusion protocols used (Fig. 1A). Of those that used fixed or combination insulin infusion protocols, only one had a fixed starting rate of 4 u/h, with the remaining protocols determining rate based on units per kilogram (u/kg); most commonly 0.1 u/kg and/or 0.05 u/kg, with one hospital using 0.07 u/kg. A few ($n = 3$, 10%) protocols included a bolus of intravenous insulin at the start of DKA management, all of which were in the variable insulin infusion cohort. The majority ($n = 21$, 68%) of protocols advised to continue basal subcutaneous insulin. Most (77%) respondents had worked at another hospital that had a different DKA management protocol. When asked about personal preference of variable versus fixed insulin infusion rates, there was a 50% split ($n = 14$ each), with three respondents not having a preference (Fig. 1B).

Location of DKA management

The primary location of DKA management was split between the emergency department ($n = 9$, 29%), ICU ($n = 8$, 26%), high dependency unit ($n = 4$, 13%) and ward ($n = 10$, 32%) (Table 2). The majority ($n = 24$, 77%) reported having protocolised criteria for ICU admission. The criteria for admission to the ICU included biochemical and clinical factors.

Fluid administration

The specification of the rate of intravenous fluids was common ($n = 26$, 84%), as was the specification of type of intravenous fluids ($n = 23$, 79%) (Table 2). The most commonly specified intravenous fluid type was 0.9% sodium chloride ($n = 19$, 86%), with three protocols specifying balanced crystalloid, all of which were in the variable insulin infusion cohort. Clinician preference was predominantly 0.9% sodium chloride ($n = 21$, 70%).

Specification of SGLT2i-associated ketoacidosis management

Just over half ($n = 17$, 55%) of DKA protocols mentioned SGLT2is; however, only five (16%) had distinct management of SGLT2i-associated ketoacidosis (Table 2).

Definition of DKA resolution

Most (67%) protocols defined resolution of DKA, with serum pH level (75%) and/or ketone level (85%) being

Table 2 Elements of DKA management protocols from Australian hospitals

	Fixed ($n = 12$)	Variable ($n = 14$)	Combination ($n = 5$)
Location where majority of DKA is managed			
ED	4	4	1
ICU	1	5	1
HDU	3	1	0
Ward	4	4	3
Bolus of intravenous insulin			
Yes	0	3	0
No	12	11	5
Continuation of basal subcutaneous insulin			
Yes	10	8	4
No	2	6	1
Specification of rate of intravenous fluids			
Yes	10	11	5
No	2	3	0
Specification of type of intravenous fluids			
Yes	8	13	4
No	4	1	1
Type of intravenous fluids specified			
0.9% sodium chloride	7	8	4
Balanced crystalloid	0	3	0
Differentiation of management of SGLT2i DKA			
Yes	3	1	1
No	9	13	4

DKA, diabetic ketoacidosis; ED, emergency department; HDU, high dependency unit; ICU, intensive care unit; SGLT2i, sodium glucose co-transporter 2 inhibitor.

the most common endpoints for resolution. Of the protocols that provided cut-off pH levels for resolution of DKA ($n = 12$), most ($n = 10$, 83%) used a pH >7.3, with two using a pH >7.35 (Fig. 2). The cut-off ketone concentration for resolution of DKA varied: from 13 respondents, two (15%) used <1.0 mmol/L, 10 (77%) used <0.6 mmol/L and one used <0.3 mmol/L.

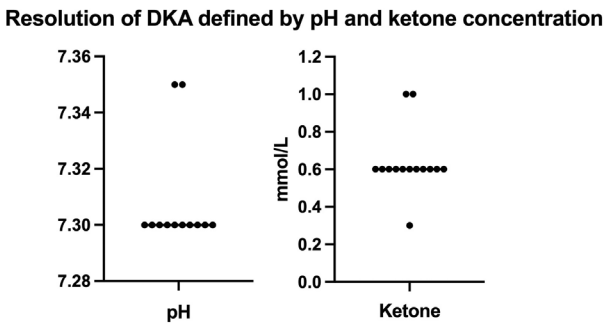

Figure 2 Resolution of diabetic ketoacidosis (DKA) defined by pH and ketone concentration, with each dot representing a unique response.

Discussion

In this survey of practice amongst endocrinologist and intensive care physicians in Australia, there was substantial variation in the local protocols for the management of DKA. The primary outcome of type of insulin infusion used for the management of DKA was highly variable, with fixed being utilised by 39%, variable by 45% and combination by 16%. Similarly, clinician preference of fixed-rate versus variable-rate intravenous insulin infusion was diverse. This likely reflects the lack of evidence of superiority of either variable or fixed intravenous insulin infusions.

There has been a recent promotion of a fixed-rate insulin infusion regimen in international guidelines and reviews.[1,2,6,13] United Kingdom (UK) data collected in 2013 showed variation in DKA diagnosis and management, including diversity in the variable-rate insulin infusion guidelines.[14] Since the establishment of the Joint British Diabetes Societies for Inpatient Care group, fixed-rate intravenous insulin infusions have been recommended for the management of DKA.[6,15] The rationale for this recommendation was due to changes in patient demographics with increasing obesity and insulin resistance, as well as the need for conformity of practice across healthcare systems; however, there are no data demonstrating superiority of one regimen over another.[15,16]

Recently, an international consortium including the American Diabetes Association, European Association for the Study of Diabetes, Joint British Diabetes Societies for Inpatient Care, American Association of Clinical Endocrinology and Diabetes Technology Society, released a consensus report on hyperglycaemic crises in adults with diabetes recommending weight-based fixed-rate intravenous insulin infusions for the management of DKA.[2] There is a suggestion in the report that a variable-rate infusion approach could be employed in certain nurse-led circumstances, based on a retrospective study of non-inferiority.[17,18] Hence, the recommendation for variable insulin infusions being limited to nurse-driven management appears tenuous.

Hypoglycaemia is a notable adverse event of insulin treatment. High rates of hypoglycaemia in 28% of people treated with fixed-rate insulin infusions for DKA in the UK in 2014 led to an update in the UK guidelines.[19] In 2022, the Joint British Diabetes Society for Inpatient Care updated their guidelines to introduce a consideration of reducing the rate of the fixed insulin infusion from 0.1 u/kg/h to 0.05 u/kg/h once glucose levels fall below 14 mmol/L.[6] The limited retrospective data that exist comparing variable versus fixed insulin infusions have shown increased rates of hypoglycaemia with fixed-rate insulin infusions.[3,4] In the absence of evidence to support

fixed-rate infusions over variable-rate infusions, it is difficult to understand why this approach is championed by some guidelines, especially when it is associated with apparently higher rates of hypoglycaemia than those observed with a variable infusion rate.

Of relevance to the optimal way to treat DKA, an Australian centre recently published their experience with variable-rate intravenous insulin infusions, showing low rates of hypoglycaemia and adequate normalisation of hyperglycaemia (glucose <10 mmol/L).[5] A variable-rate intravenous insulin infusion typically results in lower doses of insulin being administered, with rates of 2.6–3.5 u/h, as used in the study described above, compared to 7 u/h in a 70-kg person, as could be used in a fixed, weight-based insulin infusion protocol.

There was also substantial variation in the other prespecified domains of DKA management, namely the type of resuscitation fluid, the provision for SGLT2i-associated DKA, the definition of resolution and timing of transition to subcutaneous insulin. Seventy percent of respondents listed 0.9% sodium chloride as their preferred resuscitation fluid. Potential explanations for this include the ability to administer additional intravenous potassium in pre-mixed fluids, familiarity with use, relatively low cost and consideration of hyperchloremia to be a relatively minor contributor to acidaemia compared to ketosis. Surprisingly, only 67% of protocols defined resolution. When the definition of resolution was defined, it was reasonably consistent, with thresholds of ketone concentration varying from 0.3 to 1.0 mmol/L and a pH of between 7.3 and 7.35.

Approximately half of the institutions made mention of SGLT2i-associated DKA in their protocol but only 16% recommended different management (e.g. use of 10% dextrose to allow adequate insulin infusion for ketone clearance), potentially reflecting the relatively recent increase in cases and an underappreciation for delayed response with this aetiology.[10] This is an area where potential improvements to practice could be made. From a pathophysiological perspective, it is clear that SGLT2i-associated DKA has a greater tendency to euglycemia and hypoglycaemia and that ketosis is less closely linked to hyperglycaemia. This suggests that variable-rate infusions may undertreat SGLT2i-associated DKA and the incorporation of early additional dextrose in variable-rate infusions is required to allow efficacy of ketone clearance. Fixed-rate infusions for the management of SGLT2i-associated DKA are likely to necessitate additional dextrose required to avoid hypoglycaemia. Prospective randomised evidence to support this practice is lacking.

This study is limited by a small sample size with a predominance of adult endocrinologists from metropolitan public hospitals. Whilst there was a small number of individual respondents, their responses answered questions on the protocol of their workplace, which reflects a large number of institutions and a high proportion of DKA management within Australia. The selected cohort of endocrinologists and intensive care physicians, without inclusion of emergency medicine physicians, may introduce a bias in the results regarding preference of use of a specific protocol. The survey had a narrow focus with quantitative answers to allow analysis; however, there are several other aspects of DKA management such as hypokalaemia monitoring, prevention and management, which should be assessed in further research.

Australia is now one of the few countries utilising and advocating for further research on both variable-rate and fixed-rate insulin infusions. Our diverse use of insulin infusion protocols may allow us to conduct national comparisons of efficacy and safety, which, in turn, could guide practice globally. A greater evidence base is needed to either support or question international guidelines. Until further evidence is available, both fixed- and variable-rate insulin infusions should be equally advocated for. The appropriate insulin infusion protocol for each hospital should be dictated by local capacity and resources, with a focus on safety and minimisation of potential adverse events, such as hypoglycaemia or hypokalaemia.

Conclusion

In conclusion, variation in the management of DKA across Australia is highly variable and often deviates from international guidelines. However, this is likely driven by the paucity of evidence. Further comparisons of the outcomes of fixed- versus variable-rate intravenous insulin infusions are required to determine the safest and most efficacious manner to improve patient outcomes. Starting with a national consensus of DKA diagnosis and DKA resolution would facilitate comparisons in outcomes with different insulin infusion regimens. After evidence is established, a national framework would allow ease of comparison and continuity of care when patients are transferred between different hospitals. The variation in practice in Australia may allow evidence of the relative efficacy and safety of fixed- and variable-dose infusions to be generated and improve the management of DKA.

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Supporting Information

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Data S1 Supporting Information.