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Original Research

Acute Management of Diabetic Ketoacidosis in Adults at 3 Teaching Hospitals in Canada: A Multicentre, Retrospective Cohort Study

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Key Messages

- Data concerning the management of diabetic ketoacidosis in Canada are scarce.
- In this retrospective study, we found that management of diabetic ketoacidosis at 3 teaching hospitals in Edmonton, Alberta, was generally aligned with guidelines.
- Hypokalemia during management was common and, in general, potassium repletion was insufficient.
- Standardized protocols or preprinted order sets for the management of diabetic ketoacidosis may be helpful, especially in smaller centres.

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ABSTRACT

Objectives: Diabetic ketoacidosis (DKA) is a common acute complication of diabetes mellitus and is associated with significant morbidity and mortality. There is currently a paucity of data concerning the Canadian experience with DKA. We aimed to characterize the acute management and course of DKA at several Canadian hospitals.

Methods: We performed a retrospective cohort study of patients admitted to 3 teaching hospitals in Edmonton, Canada. We extracted clinical and laboratory data from the medical charts of patients admitted to general internal medicine wards or intensive care units with moderate or severe DKA.

Results: We included 103 admissions (84 patients) in our study. The majority (68.9%) had type 1 diabetes and presented with severe DKA (60.2%). In the first 24 h, the median (interquartile range) intravenous fluid received was 7.0 (5.5 to 8.8) litres; 23.3% received a priming insulin bolus, 24.3% received bicarbonate and 91.3% received potassium. Hypoglycemia was relatively rare (5.8%), but hypokalemia was common (41.7%). The median time to anion gap $\leq$12 mmol/L was 8.8 (6.0 to 12.3) h. In 27.1% of cases, intravenous insulin was stopped prior to subcutaneous insulin administration, with a median of 95 (30 to 310) min elapsing before subcutaneous insulin was given. DKA-related mortality was 2.9%.

Conclusions: The acute management of DKA was generally aligned with clinical guidelines. Areas for improvement include preventing hypokalemia by proactively increasing potassium repletion, reducing initial insulin boluses, administering subcutaneous insulin before stopping intravenous insulin and administering sodium bicarbonate judiciously. Protocols and preprinted order sets may be helpful, especially in smaller centres.

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RÉSUMÉ

Objectifs : L'acidocétose diabétique (ACD) est une complication à court terme fréquente du diabète sucré et est associée à des taux significatifs de morbidité et de mortalité. Il existe actuellement peu de données sur l'expérience canadienne en ce qui concerne l'ACD. Nous avions pour objectif de caractériser la prise en charge à court terme et l'évolution de l'ACD dans plusieurs hôpitaux du Canada.

Méthodes : Nous avons réalisé une étude de cohorte prospective auprès de patients admis dans 3 hôpitaux d'enseignement d'Edmonton, au Canada. Nous avons extrait les données cliniques et de laboratoire des dossiers médicaux des patients admis dans les salles de médecine interne générale ou dans les unités de soins intensifs en raison d'une ACD modérée ou grave.

Résultats : Nous avons tenu compte de 103 admissions (84 patients) pour notre étude. La majorité (68,9 %) des patients avaient le diabète de type 1 et présentaient une ACD grave (60,2 %). Dans les 24 premières heures, le volume médian de fluide reçu par voie intraveineuse (intervalle interquartile) était de 7,0 (5,5 à 8,8) litres; 23,3 % ont reçu un bolus d'amorçage d'insuline, 24,3 % ont reçu du bicarbonate et 91,3 % ont reçu du potassium. L'hypoglycémie était relativement rare (5,8 %), mais l'hypokaliémie était fréquente (41,7 %). Le temps médian au trou anionique $\leq$12 mmol/L était de 8,8 (6,0 à 12,3) h. Dans 27,1 % des cas, l'administration de l'insuline par voie intraveineuse était interrompue avant l'administration sous-cutanée d'insuline; un temps médian de 95 (30 à 310) min s'écoulait avant l'administration sous-cutanée d'insuline. La mortalité liée à l'ACD était de 2,9 %.

Conclusions : La prise en charge à court terme de l'ACD était généralement conforme aux lignes directrices de la pratique clinique. Les points à améliorer étaient les suivants: la prévention de l'hypokaliémie par l'augmentation proactive de la réplétion en potassium, la réduction des bolus initiaux d'insuline, l'administration sous-cutanée d'insuline avant l'interruption de l'insuline intraveineuse et l'administration judicieuse de bicarbonate de sodium. Les protocoles et les modèles d'ordonnances préimprimées peuvent être utiles, particulièrement dans les plus petits centres.

Introduction

Diabetic ketoacidosis (DKA) is a common metabolic complication of diabetes mellitus; there is an estimated annual incidence of 10 to 30 per 1,000 persons with diabetes (1–3). DKA is associated with significant morbidity and mortality, although contemporary series have reported mortality rates of 0.5% to 1.0% (1,4). Management of DKA can be complex and can be associated with a number of dangerous complications, including hypoglycemia, hyperkalemia and hypokalemia, cardiac arrhythmias and cerebral edema. In addition, hospitalization for DKA places a substantial economic burden on health-care systems (5). In many instances, DKA can be prevented by appropriate outpatient care, education and communication with primary health-care providers.

Although mild DKA may be managed in outpatients, moderate and severe DKA are most appropriately managed in the inpatient setting. In many parts of Canada, management is performed by generalist physicians who may encounter this disorder infrequently and may not be familiar with the long, detailed clinical practice guidelines (CPGs). Protocols have been developed in some centres to standardize the management of DKA, but they are not used routinely in many hospitals.

CPGs have been published by several expert committees, including Diabetes Canada (DC) and the American Diabetes Association, to help guide the management of DKA based on the best available evidence (5,6). Both CPGs provide a summary algorithm to guide management of DKA, which can be referenced easily. However, some aspects of DKA management remain controversial, and consideration of the particular clinical context is necessary.

Our goal was to describe the current management of moderate and severe DKA in patients admitted to 3 hospitals in Edmonton, Alberta, Canada, with a particular emphasis on quality of care and safety. We were also interested in exploring whether better adherence to current Canadian CPGs was associated with fewer complications of DKA treatment.

Methods

Study design and setting

We conducted a retrospective, observational cohort study of patients admitted with moderate or severe DKA at 3 hospitals in Edmonton: 2 tertiary care centres (University of Alberta Hospital and Royal Alexandra Hospital) and 1 community hospital (Misericordia Community Hospital).

Study population

Our cohort included adult patients 18 years of age or older who were admitted to a general medicine ward or an intensive care unit with primary diagnoses of moderate or severe DKA. Admissions were identified using the Alberta Health Services Data Integration and Management Repository and the following International Statistical Classification of Diseases and Related Health Problems-10 codes: E10.10, E10.12, E11.10, E11.12, E13.10, E13.12, E14.10, E14.12. At each site, we retrieved the medical records of the 50 most recent admissions, accrued retrospectively from June 30, 2014. The total time period of inclusion was from May 1, 2013, to June 30, 2014.

All types and causes of diabetes were included if diagnostic criteria for DKA were met. Patients were excluded if they were pregnant, had estimated baseline glomerular filtration rates $\leq$30 mL/min/1.73 m^2, were on dialysis or presented with hyperosmolar hyperglycemic states. The diagnosis and severity of DKA were defined according to American Diabetes Association criteria (5). Briefly, the diagnosis requires a glucose >13.9 mmol/L, positive urine or serum ketones and an anion gap >12 mmol/L. Moderate DKA was defined as arterial pH 7.0 to 7.24 or serum bicarbonate 10 to 14 mmol/L, while severe DKA was defined as arterial pH <7.0 or serum bicarbonate <10 mmol/L. When arterial blood gas data were not available, the pH was estimated by adding 0.03 to the venous blood gas pH (7). Although mental status reflects the severity of

DKA, we did not utilize it because no standardized assessment was used, and it was not consistently recorded.

Data collection and outcome measures

Data, including demographics, course in hospital, clinical data, laboratory parameters and adverse outcomes, were retrieved from medical records and recorded on case report forms. Diabetes type and duration, comorbidities, medications and precipitating factors were obtained directly from admission and discharge documentation; these data were documented by the attending physician, but no verification (including that of diabetes type) could be completed due to the retrospective nature of this study. Laboratory data included serum electrolytes, glucose, creatinine, ketones (beta-hydroxybutyrate), glycated hemoglobin, lactate, blood gases and urine ketones. Serum anion gap was calculated by subtracting chloride and bicarbonate from sodium. Bedside capillary glucose was used in most instances; however, if the glucose value was outside the detection limits of the glucometer, then glucose from serum or a blood gas was used instead. All hospitals used the Accu-Chek Inform II glucometers (Roche Diabetes Care, Indianapolis, Indiana, United States), which are regularly calibrated as per regional policies.

Study definitions

Resolution of DKA was defined as anion gap $\leq$12 mmol/L and glucose $\leq$14 mmol/L, based on the DC recommendations to maintain glucose in the 12 to 14 mmol/L range (6). We also evaluated resolution of DKA using the 2009 American Diabetes Association criteria, which require a glucose level $<$11.1 mmol/L in addition to 2 of the following: serum bicarbonate $\geq$15 mmol/L, venous pH $>$7.3 and anion gap $\leq$12 mmol/L (5).

Time 0 (start of treatment) was defined as the time at which intravenous fluid (IVF) was started in the emergency department (ED) at the original presenting hospital. IVF given by paramedics and other pretriage services was recorded and included in the calculation of total fluid given but was not used in the definition of time 0.

We defined saline solutions as those containing any amount of saline, including 0.45% saline, 0.9% saline and 0.45% saline with dextrose. We defined dextrose solutions as those that contained only dextrose. The volume of blood products and fluid from insulin infusions and medications was not included in the total fluid calculations. As hourly totals of fluid administered were not always recorded, in some instances the fluid totals were extrapolated using the most recent hourly rate until there was a recorded change in rate. Hypoglycemia was defined as glucose $<$4 mmol/L. Hyperkalemia was defined as potassium $>$5 mmol/L, and significant hyperkalemia was defined as potassium $>$6 mmol/L. Hypokalemia was defined as potassium $<$3.5 mmol/L. When calculating amounts of potassium and phosphate supplementation received, all sources (including resuscitation and maintenance fluids) and routes (oral and intravenous) were included in the total.

Statistical analysis

Statistical analysis was performed using Stata 15.1 (StataCorp, College Station, Texas, United States). Continuous variables are presented as mean (standard deviation) for parametric data or median (interquartile range) for nonparametric data. Means were compared using the t test, and medians were compared using the Wilcoxon rank sum test. Proportions were compared using the chi-square test.

Ethics approval

Ethics approval was obtained from the Research Ethics Board at the University of Alberta (#Pro00052315).

Results

A total of 103 admissions (84 unique patients) were included in our study, as illustrated in Figure 1. We retrieved medical records at

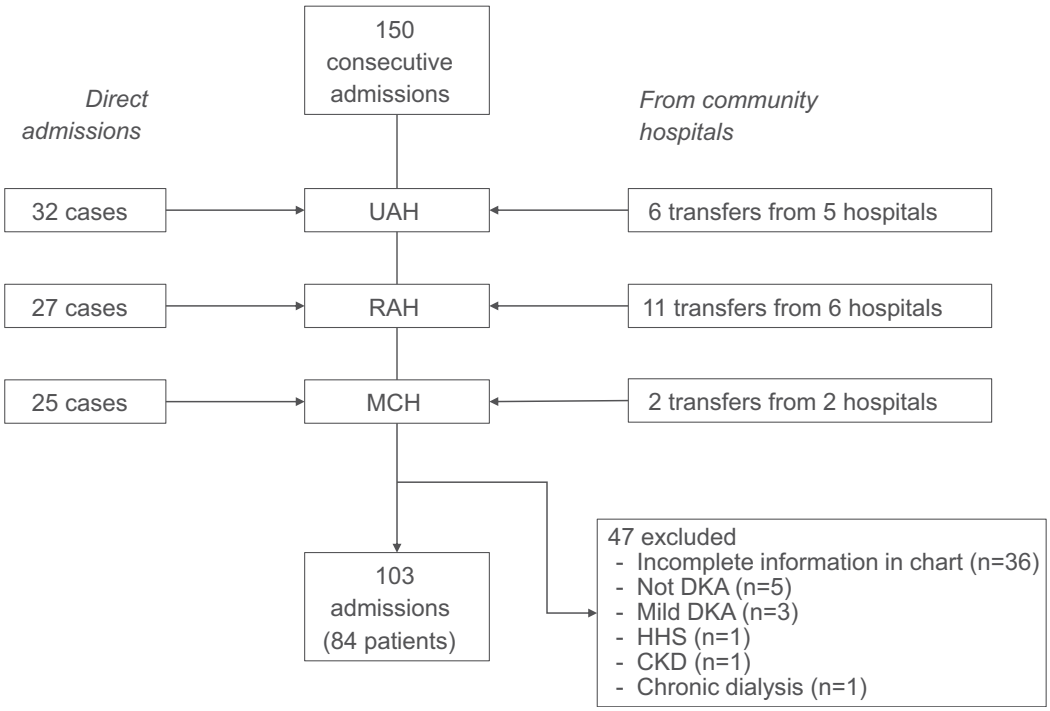

Figure 1. Study design and included cases. *CKD*, chronic kidney disease; *DKA*, diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycemic state; *MCH*, Misericordia Community Hospital; *RAH*, Royal Alexandra Hospital; *UAH*, University of Alberta Hospital.

3 main hospitals, but 19 admissions (18.4%) were transferred from community hospitals (14 centres in total).

In all cases, initial management was performed by an ED physician. Patients with DKA are not admitted to family medicine wards at any of the 3 main hospitals, so subsequent care was generally performed by an internist, except when patients were admitted to the intensive care unit. At the 2 tertiary care hospitals, general medicine beds that can support more intensive monitoring and therapy (sometimes called step-up units) are available, and patients were usually transferred to these beds once admitted (unless the beds were already occupied). At the community hospital, patients remained in the ED (under internist care) until intensive monitoring and therapy were no longer required; they were then transferred to the general medicine ward. A resident physician was involved in patient care in at least 95% of cases (trainee status was not always available), and a nurse practitioner was involved in 9.7% of cases. At all sites, endocrinologists served in consultant roles and, thus, were not usually directly responsible for DKA management, although they may have been involved in complex cases, transitions to subcutaneous insulin or definitive diagnoses. Finally, at transferring hospitals (when patients were not admitted), patient care was performed by ED physicians, with paramedics providing care during transfer.

The baseline clinical characteristics of all admissions are shown in Table 1, and comorbidity and medication data are shown in Supplementary Tables 1 and 2. Admission parameters are shown for each hospital individually in Supplementary Table 3. Overall, the mean age was 38.7 (15.1) years, and 56% were male; the majority had type 1 diabetes, but 24.3% had type 2 diabetes. The majority (60.2%) of admissions were for severe DKA, and only 10% were admitted to an intensive care unit. Cardiovascular, cerebrovascular and peripheral vascular disease were relatively uncommon in our cohort (13.6% combined). Few patients were taking metformin (15.5%) and no patients were taking sodium-glucose cotransporter 2 inhibitors.

Table 1
Baseline characteristics of patients admitted with moderate or severe diabetic ketoacidosis

Variable	All cases (n=103)	Moderate DKA (n=41)	Severe DKA (n=62)	p value†
Age (years)	38.7 (15.1)	42.0 (15.4)	36.5 (14.7)	0.07
Male sex, n (%)	58 (56%)	24 (59%)	34 (55%)	0.71
BMI (kg/m^2)	25.5 (7.2)	25.6 (4.8)	25.5 (8.3)	0.94
A1C (%)	11.1 (2.2)	10.8 (2.3)	11.2 (2.2)	0.60
Type of diabetes				
Type 1 diabetes	71 (68.9%)	29 (70.7%)	42 (67.7%)	0.75
Type 2 diabetes	25 (24.3%)	9 (22.0%)	16 (25.8%)	0.66
Secondary diabetes or unknown	7 (6.8%)	3 (7.3%)	4 (6.5%)	0.86
Duration of diabetes (years)	10 (4–18)	13 (6–19)	8 (3–18)	0.16
Baseline eGFR (mL/min/1.73 m^2)	110 (22)	104 (23)	114 (21)	0.029
Precipitant*				
Nonadherence	36 (35.0%)	12 (29.3%)	24 (38.7%)	0.33
Intercurrent infection	34 (33.0%)	16 (39.0%)	18 (29.0%)	0.29
Unknown	28 (27.2%)	12 (29.3%)	16 (25.8%)	0.70
Alcohol or drug use	20 (19.4%)	6 (14.6%)	14 (22.6%)	0.32
New diagnosis of diabetes	11 (10.7%)	4 (9.8%)	7 (11.3%)	0.81
Financial reasons	4 (3.9%)	1 (2.4%)	3 (4.8%)	0.54
Cardiac disease	2 (1.9%)	0 (0%)	2 (3.2%)	0.25
Other‡	10 (9.7%)	4 (9.8%)	6 (9.7%)	0.99
Presentation*				
Nausea, vomiting or abdominal pain	71 (70.0%)	30 (73.2%)	41 (66.1%)	0.45
Metabolic decompensation§	39 (37.9%)	15 (36.6%)	24 (38.7%)	0.83
Altered level of consciousness	15 (14.6%)	7 (17.1%)	8 (12.9%)	0.56
Respiratory symptoms	11 (10.7%)	0 (0%)	11 (17.7%)	0.0043
Chest pain	6 (5.8%)	2 (4.9%)	4 (6.5%)	0.74
Fever	4 (3.8%)	1 (2.4%)	3 (4.8%)	0.54
Other¶	21 (20.4%)	8 (19.5%)	13 (21.0%)	0.86

A1C, glycated hemoglobin; *BMI*, body mass index; *DKA*, diabetic ketoacidosis; *eGFR*, estimated glomerular filtration rate.
Note: Data are presented as mean (standard deviation) or median (interquartile range).
* More than 1 category may apply for each patient.
† p values comparing moderate to severe DKA.
‡ Includes upper gastrointestinal bleed, diabetic enteropathy, pancreatitis, esophagitis, new diagnosis of lung cancer, insulin pump malfunction, inferior vena cava thrombosis, rape and eating disorder.
§ Includes polyuria, polydipsia, weight loss, self-reported hyperglycemia, or dehydration.
¶ Includes diarrhea, nonspecific neurologic symptoms, flank pain, flu-like symptoms, coffee-ground emesis and symptoms of cellulitis.

Initial treatment (first 24 h)

Admission parameters, initial management and course in hospital are shown in Table 2 and Table 3, and laboratory data are illustrated in Supplementary Figure 1. No patients in our cohort presented with glucose <14 mmol/L. Nearly a quarter of the patients received an insulin bolus, and one-third of these were given subcutaneously (SC). The initial infusion rate was no different in those who received a bolus and those who did not (5.0 [2.9] vs. 5.1 [2.4] units/h; p=0.85). Two patients presented with initial potassium levels <3.3 mmol/L, and insulin was not held in either case. Overall, 91% of cases received potassium supplementation in the first 24 h; among those still admitted at 72 h, the total cumulative dose of potassium was 160.4 (107.8 to 284.6) mmol (1.8 [1.0 to 3.8] mmol/kg). Excluding the presenting potassium, 27 cases (26.2%) had hyperkalemia in the first 24 h, but only 16 cases (15.5%) had significant hyperkalemia (Supplementary Table 4). Intravenous bicarbonate was given in nearly a quarter of cases, almost always (91.3%) as bolus doses. Bicarbonate was given to 2 patients with moderate DKA (pH >7) at serum bicarbonate levels of 17.0 and 15.1 mmol/L, respectively. The vast majority of IVF received at 24 h was saline (86.9%); dextrose and Ringer lactate each composed 6.0% of the total IVF received, while Plasma-Lyte A was only 1.1%. The amount of IVF received at various time points is shown in Supplementary Table 5.

Complications

Almost half (41.7%) of patients had hypokalemia in the first 24 h. Hypoglycemia was relatively uncommon in the first 24 h (5.8%), but increased with the duration of admission (cumulative prevalence 48.7% by 72 h, when most subjects had transitioned to SC insulin). There were 5 deaths in our cohort, including 3 deaths related to DKA (DKA-related mortality 2.9%) and 2 deaths related to underlying malignancy. One patient was admitted with ongoing seizures and required cardiopulmonary resuscitation; 1 patient experienced torsades de pointes in the ED. There were no cases of cerebral edema.

Subsequent care

Overall, the median time until resolution of DKA was nearly 9 h and was longer in those with severe DKA. Time until SC insulin administration was approximately 20 h. In the majority of cases, IV insulin was stopped after SC insulin was initiated; however, in 27.1% of cases, IV insulin was stopped prior to SC insulin initiation. Of the patients discharged on insulin and for whom data were available (92 in total) (Supplementary Table 6), 78 (84.8%) were receiving multiple daily insulin injections, 8 (8.7%) were on long-acting insulin only and 6 (6.5%) were on an insulin mix. Of those receiving multiple daily insulin injections whose doses were available (46 in total), the mean total daily dose was 55.8 (21.0) units (0.77 [0.33] units/kg) and the basal-to-bolus split was 56% to 44%.

Table 2
Presentation and initial management of diabetic ketoacidosis in hospital

Variable	All admissions (n=103)	Moderate DKA (n=41)	Severe DKA (n=62)	p value*
Admission duration† (h)	50.2 (31.8–109.0)	42.4 (30.6–107.5)	56.4 (34.6–108.5)	0.33
Triage vitals‡				
Temperature (°C)	36.4 (36.0–36.7)	36.5 (36.0–36.8)	36.3 (35.9–36.7)	0.16
Systolic blood pressure (mmHg)	129 (115–146)	129 (119–140)	132 (114–149)	0.68
Diastolic blood pressure (mmHg)	82 (68–93)	81 (70–91)	82 (64–95)	0.84
Heart rate (bpm)	113 (99–125)	112 (97–125)	114 (99–125)	0.68
Received vasopressors	4 (3.8%)	0 (0%)	4 (6.5%)	0.097
Initial laboratory parameters				
Capillary blood glucose (mmol/L)	29.0 (21.8–37.7)	27.0 (21.2–34.0)	31.5 (23.6–40.0)	0.11
Venous blood pH§	7.15 (7.00–7.26)	7.28 (7.23–7.33)	7.05 (6.95–7.15)	<0.001
Serum anion gap (mmol/L)	23 (19–27)	20 (18–24)	24 (21–30)	<0.001
Serum β-hydroxybutyrate (mmol/L)	5.6 (4.6–6.2)	5.8 (4.4–6.2)	5.6 (4.6–6.2)	0.64
Serum sodium (mmol/L)	134 (130–137)	133 (130–136)	134 (130–138)	0.49
Serum potassium (mmol/L)	5.0 (4.3–5.6)	4.6 (4.3–5.2)	5.1 (4.3–5.9)	0.049
Serum chloride (mmol/L)	100 (93–104)	98 (93–102)	101 (92–106)	0.17
Serum bicarbonate (mmol/L)	8.8 (4.5–14.7)	15.6 (13.1–17.0)	5.4 (4.0–7.7)	<0.001
Serum lactate (mmol/L)	2.7 (2.0–4.2)	3.1 (2.1–5.2)	2.7 (1.9–4.1)	0.54
Effective serum osmolality¶ (mmol/kg)	296 (290–307)	293 (288–301)	299 (291–309)	0.077
Initial management				
Minutes from triage until IVF started	77 (34–135)	84 (54–161)	70 (21–118)	0.054
Minutes from IVF until insulin started	25 (0–80)	27 (0–100)	21 (0–75)	0.26
Insulin bolus given, n (%)	24 (23.3%)	8 (19.5%)	16 (25.8%)	0.46
Insulin bolus, as SC, n (%)	8 (33.3%)	5 (62.5%)	3 (18.8%)	0.032
Insulin bolus, as IV, n (%)	16 (66.7%)	3 (37.5%)	13 (81.3%)	0.032
Insulin bolus amount (units)	8.1 (2.9)	8.0 (3.5)	8.2 (2.6)	0.88
Insulin bolus amount (units/kg)	0.12 (0.05)	0.11 (0.06)	0.12 (0.05)	0.86
Insulin rate start (units/h)	5.1 (2.5)	4.6 (2.5)	5.4 (2.4)	0.093
Insulin rate start (units/kg/h)	0.07 (0.03)	0.06 (0.03)	0.08 (0.03)	0.044
Pretriage IVF received, n (%)	18 (17.5%)	5 (12.2%)	13 (21.0%)	0.25
Amount received (mL)	400 (250–600)	300 (250–400)	500 (250–750)	0.30

DKA, Diabetic ketoacidosis; *IVF*, intravenous fluid; *IV*, intravenous; *SC*, subcutaneous.
Note: Data are presented as mean (standard deviation) or median (interquartile range).
* p values comparing moderate to severe DKA.
† Admission duration calculated based on the time of admission to the time of discharge, and may not include the entire time spent in the emergency department.
‡ Triage vitals at the initial presenting hospital.
§ Venous pH was calculated by subtracting 0.03 from arterial pH.
¶ Effective serum osmolality calculated as 2 × Na + glucose.

Discussion

In this study, we found that physicians treated DKA appropriately, giving first priority to prompt fluid resuscitation followed by administration of insulin. Approximately 7 litres (roughly equivalent to the estimated fluid deficit of 100 mL/kg in DKA [8]) of IVF were administered in the first 24 h, while insulin therapy was initiated about 25 min after IVF initiation. Although hypoglycemia was uncommon in the first 24 h, almost half of subjects experienced hypokalemia. The overall DKA-related mortality rate (2.9%) was slightly higher than recent series indicate (1,4), which may be related to our small sample size and the inclusion of sicker patients.

Current clinical management of moderate and severe DKA generally aligned with Canadian CPGs. Although resolution of DKA is not defined by the DC guidelines, many practitioners use the anion gap for this purpose. In our study, it took about 5 h for glucose to reach 14 mmol/L, when the addition of dextrose is recommended, and about 9 hours for normalization of the anion gap and serum bicarbonate. These data are in line with other studies (9–11) and emphasize that other diagnoses or inadequate treatment of DKA should be considered if DKA persists long after these times.

We found four areas for potential improvement.

1. Hypokalemia was common (41.7%), and potassium replacement was insufficient (1.2 mmol/kg at 24 h), findings similar to those of a study conducted at St. Michael's Hospital in Toronto (12). This may reflect a disproportionate anxiety about the risk of hyperkalemia, despite the substantial total body deficit of potassium in DKA (3 to 5 mmol/kg) (8) and the expected movement of potassium into cells with insulin administration and correction of acidemia. Hypokalemia can have serious consequences, including fatal cardiac arrhythmias. DC guidelines provide clear guidance for managing significant hypokalemia, including holding insulin and treating aggressively when potassium levels are <3.3 mmol/L. However, in the eukalemic range, the guidelines are less precise, suggesting a range of potassium concentrations (10 to 40 mmol/L) for replacement and a range of thresholds (<5.0 to 5.5 mmol/L) to start replacement. In contrast, British CPGs recommend using IVF containing 40 mmol/L of potassium when potassium is 3.5 to 5.5 mmol/L (13). DC guidelines may inadvertently create the impression that care is required to avoid hyperkalemia, when hypokalemia is the far more likely complication. Furthermore, patients with hypokalemia were generally treated with intravenous boluses, such that our data demonstrate a reactive, rather than a preventive, approach to hypokalemia.
2. A priming insulin dose (which had been recommended historically) was given in nearly a quarter of cases. A recent trial showed equivalency between a bolus and infusion as long as the infusion was started at a higher rate (0.14 units/kg/h) (14), and many guidelines (including DC) now recommend against an insulin bolus (6,13).
3. Although guidelines recommend that SC insulin be given at least 1 to 2 h before IV insulin is stopped, so as to prevent recurrence of hyperglycemia and ketoacidosis (5), IV insulin was discontinued before any SC insulin was given in a quarter of the cases. In these cases, the median time until SC insulin was given was 95 min; IV insulin has a half-life of only minutes (15), so it is concerning that these patients would be without insulin for prolonged periods of time.

Table 3
Course of diabetic ketoacidosis in hospital

Variable	All admissions (n=103)	Moderate DKA (n=41)	Severe DKA (n=62)	p value*
In the first 24 h				
Patients with at least 1 glucose <4 mmol/L	6 (5.8%)	3 (7.3%)	3 (4.8%)	0.60
Patients with initial K <3.3 mmol/L	2 (1.9%)	1 (2.6%)	1 (1.7%)	0.75
Patients with at least 1 K <3.5 mmol/L	43 (41.7%)	14 (34.1%)	29 (46.8%)	0.20
Patients with at least 1 K <3.3 mmol/L	23 (22.3%)	7 (17.1%)	16 (25.8%)	0.30
Total K given (mmol)	89.5 (48.0–127.8)	71.3 (20.0–115.5)	93.2 (59.8–138.0)	0.053
Total K given (mmol/kg)	1.22 (0.55–1.79)	0.73 (0.17–1.71)	1.31 (0.76–1.91)	0.028
Patients not given any K	9 (8.7%)	6 (14.6%)	3 (4.8%)	0.085
Patients given bicarbonate	25 (24.3%)	2 (4.9%)	23 (37.1%)	<0.001
Bicarbonate given (mmol)	100 (50–200)	199 (198–200)	100 (50–200)	0.24
Nadir serum bicarbonate (mmol/L)	6.25 (4.0–10.4)	15.4 (13.6–19.9)	4.4 (3.7–8.3)	0.0031
Nadir venous pH	7.00 (6.90–7.11)	7.27 (7.16–7.35)	6.98 (6.88–7.04)	0.0046
Patients given phosphate	14 (13.6%)	2 (4.9%)	12 (19.4%)	0.036
Phosphate given (mmol)	16.0 (15.0–30.0)	22.5 (15.0–30.0)	16.0 (15.0–37.5)	0.77
IVF received (litres)	7.0 (5.5–8.8)	6.2 (5.4–7.4)	7.7 (6.2–9.3)	0.0089
0.9% saline (% of total)	86.9%	89.8%	85.1%	0.19
Ringer lactate (% of total)	6.0%	3.9%	7.3%	0.21
Plasma-Lyte A (% of total)	1.1%	0.6%	1.5%	0.37
Dextrose† (% of total)	6.0%	5.7%	6.1%	0.85
DKA resolution				
Time until AG ≤12 mmol/L (hours)	8.8 (6.0–12.3)	7.2 (4.5–10.9)	9.3 (6.8–12.7)	0.03
Time until glucose ≤14 mmol/L (hours)	5.2 (3.3–9.1)	4.3 (2.8–8.0)	5.8 (3.9–9.6)	0.11
Time until bicarbonate ≥15 mmol/L (hours)	9.2 (5.4–15.8)	4.8 (2.4–8.1)	11.8 (8.6–18.0)	<0.001
Time until venous pH ≤7.3 (h)	7.2 (4.3–12.3)	4.5 (3.4–6.6)	10.7 (5.4–15.8)	0.0034
Time until dextrose started (h)	5.0 (3.2–8.8)	3.9 (2.4–9.3)	5.3 (3.7–8.7)	0.25
Glucose (mmol/L) when dextrose started	13.7 (11.0–16.3)	13.7 (10.8–16.2)	13.7 (11.0–16.5)	0.84
Transition to SC insulin				
Time until transition (h)	20.6 (13.5–28.3)	18.7 (12.2–23.1)	23.3 (16.1–34.5)	0.041
IV stopped after SC	62 (72.9%)	23 (63.9%)	39 (80.0%)	0.11
IV-SC overlap (minutes)	60 (16–82)	65 (55–115)	55 (0–80)	0.17
IV stopped before SC	23 (27.1%)	13 (36.1%)	10 (20.0%)	0.11
Time until SC given (minutes)	95 (30–310)	105 (60–310)	55 (15–145)	0.088
SC insulin used for transition				
Rapid-acting only	43 (45.7%)	12 (30.8%)	31 (56.4%)	0.014
Long-acting only	32 (34.0%)	12 (30.8%)	20 (36.4%)	0.57
Rapid- and long-acting	19 (20.2%)	15 (38.5%)	4 (7.3%)	<0.001

AG, Anion gap; *DKA*, diabetic ketoacidosis; *IV*, intravenous; *K*, potassium; *SC*, subcutaneous.
Note: Data are presented as mean (standard deviation) or median (interquartile range).
* p values comparing moderate to severe DKA.
† Dextrose fluids are defined as those containing only dextrose (without saline or Ringer lactate).

4. The role of bicarbonate administration in the management of DKA is controversial (5,6,16). DC guidelines recommend that bicarbonate be considered as a slow infusion (as opposed to a bolus) when pH is <7.0. In our study, bicarbonate was given to nearly a quarter of patients (almost always as a bolus), including to 2 patients with moderate DKA who did not have severe acidosis.

In our series, nearly one-fifth of cases were transferred from smaller centres, largely because of insufficient resources for intensive monitoring of therapy. Only 1 centre (a community hospital) of all 14 included had a standardized protocol to guide DKA management as recommended by Canadian CPGs. DKA management can be complex, and the consequences of mismanagement can be severe; given Canada's geography, transfer criteria and simple guidelines (in the form of preprinted order sets or protocols), especially for low-volume centres, may be of particular importance.

DKA is considered an ambulatory care-sensitive diagnosis. In our series, baseline glycemic control was poor (mean glycated hemoglobin levels of 11.1%), and inadequate adherence was the most common precipitant of DKA, in line with other series (10,17,18). Furthermore, numerous patients had recurrent DKA. Therefore, it appears that there is potential to prevent some cases of DKA with increased education and support for patients and health-care providers. Furthermore, type 2 diabetes represented a quarter of our cases, similar to the 20% to 35% reported in the literature (5,10,19–21), and given that type 2 diabetes is much more common in adults than type 1 diabetes, additional education about the risk for DKA in type 2 diabetes seems prudent.

Our study is an important addition to the current literature concerning DKA, particularly in the Canadian context. To our knowledge, this is the first substantial study to evaluate DKA management at several hospitals in Canada. We have observed that, although management of DKA was quite good overall, there are several areas for potential improvement that clinicians may be able to implement in their practices. Furthermore, our data suggest that potassium repletion strategies in Canadian CPGs may be inadvertently contributing to hypokalemia.

Limitations

As is typical of retrospective case series, there are several limitations in our study that should be considered. Data were obtained from medical chart reviews, so we were not able to verify or standardize definitions of such items as precipitating factors, medications and comorbidities. Laboratory investigations and management practices were not standardized across the sites and varied by treating provider, but all laboratory data are available through a provincial electronic health database such that we likely have very few missing data. We included only cases of moderate or severe DKA that were admitted to hospital, and our results may not be applicable to patients with mild DKA who do not require admission to hospital. Our findings may not be generalizable to other parts of Canada or internationally.

Conclusions

The management of moderate and severe DKA at 3 hospitals in Edmonton was generally aligned with DC guidelines and with other international series. Areas for potential improvement include more aggressive and proactive potassium repletion, less use of a priming insulin bolus, administering SC insulin at least 1 h to 2 h before IV insulin is stopped, and the avoidance of sodium bicarbonate in situations where its use is not recommended. The creation and implementation of a standardized protocol for referring hospitals may be helpful in improving the quality and safety of DKA management, while ongoing education and support of patients will be important to prevent some cases of DKA.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

Author Disclosures

PAS was a member of the Diabetes Canada 2018 Clinical Practice Guidelines Steering Committee and cochair of the Diabetes Canada Professional Section. The views expressed in the manuscript are his own and do not represent those of Diabetes Canada. No other conflicts of interest related to this study are reported by any of the authors.

Author Contributions

BPG and SMB originally conceived of the study; BPG retrieved the data from medical records and wrote the first draft of the report; all authors were involved in study design, analysis of the data and interpretation of the results; all authors revised the manuscript critically for important intellectual content, agreed on the final content of the manuscript and agreed to be accountable for all aspects of the work.

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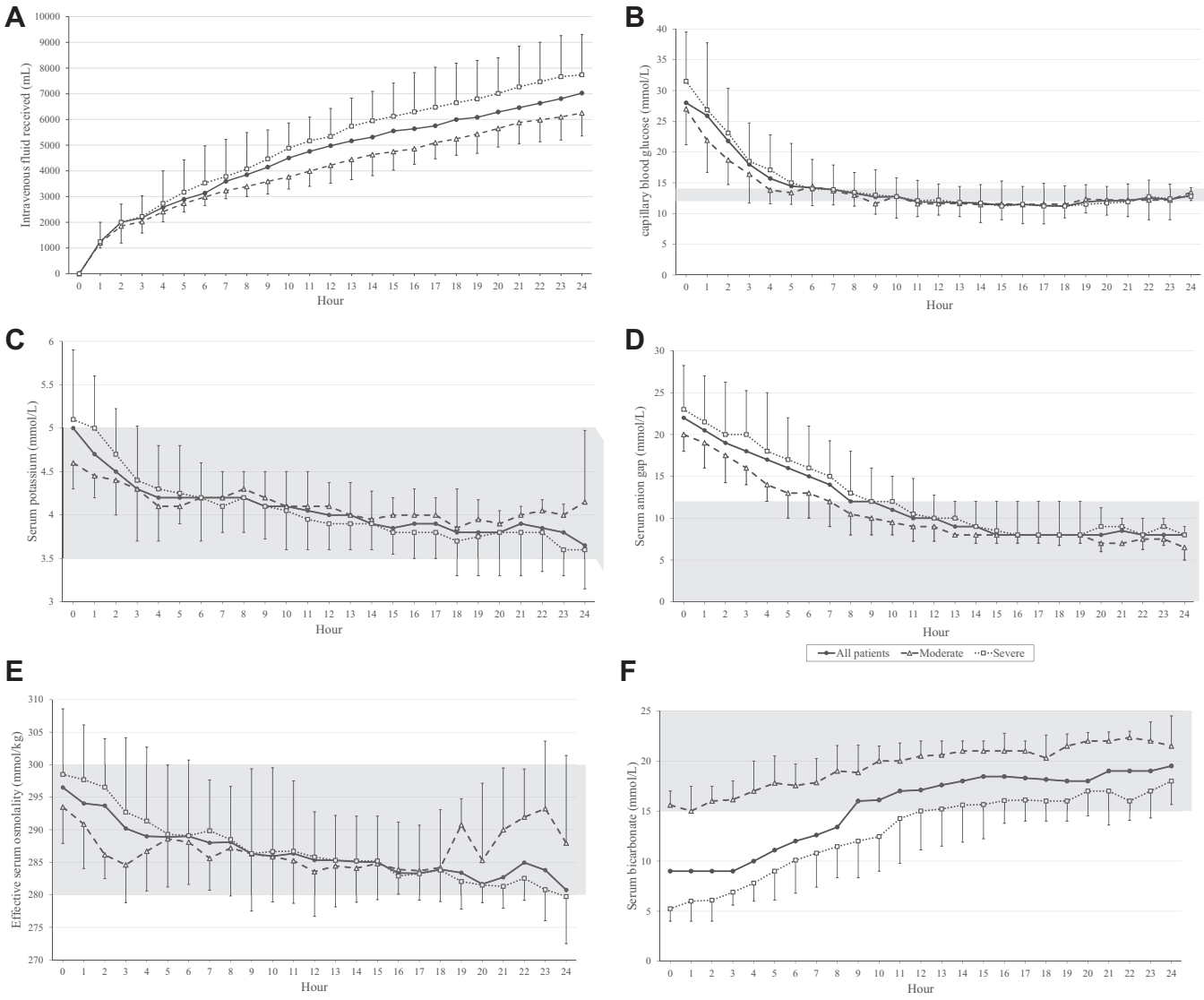

Supplementary Figure 1. Total cumulative intravenous fluid administration (A) and biochemical parameters (B through F) of all cases (●); moderate DKA (△) and severe DKA (▫), shown as medians with interquartile ranges. Shaded bars represent the target range for glucose (B) as per Diabetes Canada guidelines (12–14 mmol/L), the normal range for potassium (C) (3.5–5.0 mmol/L) and effective serum osmolality (E) (280–300 mmol/kg) and the cut-offs for resolution of DKA as per ADA guidelines for anion gap (D) (≤12 mmol/L) and bicarbonate (F) (≥15 mmol/L). *ADA*, American Diabetes Association; *DKA*, diabetes ketoacidosis.

Supplementary Table 1
Comorbidities of admitted patients

	All admissions (N=103)
Hypertension	27 (26.2%)
Dyslipidemia	24 (23.3%)
Alcohol use	28 (27.2%)
Drug abuse	12 (11.7%)
Smoking	15 (14.6%)
CAD, CVA, CHF, PAD	14 (13.6%)
CAD	4 (3.9%)
CHF	2 (1.9%)
CVA	6 (5.8%)
PAD	2 (1.9%)
Celiac disease	1 (1.0%)
Hypothyroidism	12 (11.7%)
Addison disease	1 (1.0%)
Previous pancreatitis	14 (13.6%)

CAD, Coronary artery disease; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident; *PAD*, peripheral arterial disease.

Supplementary Table 2
Medication use at time of admission

	All admissions (N=103)
Metformin	16 (15.5%)
Total daily dose (mg)	1766 (460)
Sulphonylureas	4 (3.9%)
Statins	28 (27.2%)
ACEi or ARB	27 (26.2%)
Beta blocker	10 (9.7%)
ASA	12 (11.7%)
Levothyroxine	9 (8.7%)

ACEi, Angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *ASA*, acetylsalicylic acid.

Supplementary Table 3
Admissions at individual hospitals

	RAH (n=38)	UAH (n=38)	MCH (n=27)
Transfer from community hospital	11 (28.9%)	6 (15.8%)	2 (7.4%)
Severe DKA	26 (68.4%)	19 (50%)	17 (63.0%)
ICU admission	3 (7.9%)	5 (13.2%)	2 (7.4%)
Admission duration (h)	58.8 (38.3–109.5)	39.2 (22.0–102.7)	61.3 (32.6–136.6)
Triage to IVF (min)	49.0 (18.0–113.0)	79.0 (50.0–126.0)	92.5 (68.5–212.5)
IVF to insulin (min)	25.0 (0–75.0)	15.5 (0–80.0)	68.0 (0–101.0)
Insulin bolus, n (%)	10 (26.3%)	5 (13.2%)	9 (33.3%)
Insulin bolus (units)	8.0 (2.6)	7.8 (2.2)	8.4 (3.7)
Total fluid received at 24 h (litres)	7.7 (5.6–9.4)	6.9 (5.8–9.0)	6.4 (5.1–7.7)
Time to AG of 12 (h)	8.7 (6.0–11.0)	6.7 (3.9–9.8)	12.0 (9.1–17.1)

AG, Anion gap; *DKA*, diabetic ketoacidosis; *ICU*, intensive care unit; *IVF*, intravenous fluid; *MCH*, Misericordia Community Hospital; *RAH*, Royal Alexandra Hospital; *UAH*, University of Alberta Hospital.

Supplementary Table 4
Potassium levels during course of hospitalization

	All admissions (N=103)
Any potassium >5 mmol/L	52 (50.5%)
Any potassium >5 mmol/L, excluding initial	27 (26.2%)
Any potassium >6 mmol/L, excluding initial	16 (15.5%)
Max potassium (mmol/L)	8.3
Max potassium (mmol/L), excluding initial	8.3
Nadir potassium (mmol/L)	2.2

Supplementary Table 5
Intravenous fluid (litres) received at various time points during hospitalization

	All admissions (n=103)
6 h	3.1 (2.7–4.4)
12 h	5.0 (3.8–5.9)
24 h	7.0 (5.5–8.8)
48 h	10.2 (7.5–12.9)
72 h	13.3 (9.6–15.7)

Supplementary Table 6
Insulin therapy at discharge

	Data available (N=92)
Multiple daily injections	78 (84.8%)
Total daily dose, units	55.8 (21.0)
Total daily dose, units per kg	0.77 (0.33)
Basal:bolus split	55.6%/44.5%
Glargine	70 (76.1%)
Detemir	6 (6.5%)
N/NPH	10 (10.9%)
Aspart	39 (45.9%)
Lispro	37 (43.5%)
Glulisine	1 (1.2%)
R/Toronto	2 (2.4%)
30/70 mix	3 (3.3%)
Lispro mix	3 (3.3%)