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Presenting Predictors and Temporal Trends of Treatment-Related Outcomes in Diabetic Ketoacidosis

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Abstract

Objective: This study examines temporal trends in treatment-related outcomes surrounding a diabetic ketoacidosis (DKA) performance improvement intervention consisting of mandated intensive care unit admission and implementation of a standardized management pathway, and identifies physical and biochemical characteristics associated with outcomes in this population.

Methods: A retrospective cohort of 1,225 children with DKA were identified in the electronic health record by International Classification of Diseases codes and a minimum pH less than 7.3 during hospitalization at a quaternary children's hospital between April 2009 and May 2016. Multivariable regression examined predictors and trends of hypoglycemia, central venous line placement, severe hyperchloremia, head computed tomography (CT) utilization, treated cerebral edema and hospital length of stay (LOS).

Results: The incidence of severe hyperchloremia and head CT utilization decreased during the study period. Among patients with severe DKA (presenting pH<7.1), the intervention was associated with decreasing LOS and less variability in LOS. Lower pH at presentation was independently associated with increased risk for all outcomes except hypoglycemia, which was associated with higher pH. Patients treated for cerebral edema had a lower presenting mean systolic blood pressure z score (0.58 [95% confidence interval -0.02–1.17] versus 1.23 [1.13–1.33]) and a higher maximum mean SBP z score during hospitalization (3.75 [3.19–4.31] versus

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2.48 [2.38–2.58]) compared to patients not receiving cerebral edema treatment. Blood pressure and cerebral edema remained significantly associated after covariate adjustment.

Conclusion: Treatment-related outcomes improved over the entire study period and following a performance improvement intervention. The association of SBP with cerebral edema warrants further study.

Introduction

Diabetic ketoacidosis (DKA) is the most serious acute complication of Type 1 diabetes and is associated with an estimated annual treatment cost of \$90 million in the United States among children and adolescents.(1) Consensus guidelines for DKA outline management strategies based on the best-available evidence with the aim of optimizing outcomes, though these guidelines also note existing equipoise, stating “no treatment strategy can be definitively recommended as being superior to another based on current evidence.”(2) Institutional adoption of standardized approaches to DKA treatment based on these guidelines have been reported to reduce management variability and lead to improved outcomes, though limitations of these observational studies include small sample size, lack of comprehensive biochemical data and before-after analyses that do not account for management trends over time.(3–5)

The electronic health record (EHR) and computerized order entry have been used to facilitate uniformity in the management of DKA through order sets and decision-support.(3) Spurred by Meaningful Use Incentives, the emergence of electronic health data collection and storage has generated large repositories of structured data elements harbored by many institutions that can be readily searched and continue to accumulate.(6) The Institute of Medicine has recognized the potential of leveraging such data sources to support research endeavors and performance improvement initiatives as part of the strategic development of learning health care systems.(7–10) Granular patient-level EHR data can be examined to elucidate elements of disease pathophysiology, such as the development of DKA-related cerebral edema, within large, readily available cohorts. This approach provides an opportunity to replicate and further validate the findings of smaller, sentinel studies and to explore the significance of incompletely understood disease features such as the presence of hypertension in children with DKA.(11)

We sought to examine temporal trends in the management of DKA at our institution between 2009 and 2016 and identify presenting characteristics associated with treatment-related outcomes by querying an EHR-derived data warehouse. We hypothesized that system-level changes in care, including mandating pediatric intensive care unit (PICU) admission for DKA management and implementation of a standardized management pathway and order set based on international consensus guidelines, would be associated with improved outcomes during this period.(2) Additionally, given that hypertension is common among children with DKA, even among those who do not experience neurologic decompensation, a secondary objective was to determine whether presenting blood pressure and maximum blood pressure during hospitalization are associated with treatment for cerebral edema in this population.

Methods

Study Design and Setting

This is a single-center, retrospective cohort study of patients with DKA identified using structured EHR data. Approval was granted by the University of Pittsburgh Medical Center quality improvement (QI) project review board, an oversight body responsible for ensuring QI projects meet appropriate ethical standards, and by the University of Pittsburgh Institutional Review Board. The study center is a 296-bed quaternary children's hospital that is the main referral center for pediatric subspecialty care and acute childhood diseases in a region of approximately 5 million people. Patients with DKA are cared for by attending pediatric intensivists, endocrinologists, nurse practitioners/physician assistants and all levels of trainees, including pediatric residents and both endocrinology and critical care fellows. Our institution also has an active regional patient transport program with prehospital care of all transferred patients guided by a pediatric critical care fellow, either by phone or in-person. Our EHR does not readily distinguish patients who present initially to our institution versus being transferred from a referring institution.

The primary goal of this study was to examine outcomes surrounding two systematic changes in our institution's management of DKA. In April 2012, our institution mandated that all patients with DKA requiring an insulin infusion be admitted to the PICU until sufficient resolution of DKA allowed for transition to a maintenance subcutaneous insulin regimen. In December 2012, an evidence-based DKA guideline outlining management of intravenous fluid and dextrose titration was made available to all clinicians at our institution (Supplemental Box 1). Outcomes of interest were selected based on investigator consensus regarding potentially modifiable, clinically significant treatment-related complications and components of management. Outcomes included the incidence of cerebral edema (defined as administration of either 3% aqueous saline or mannitol), hypoglycemia (serum glucose <70 mg/dL), severe hyperchloremia (serum chloride >120 mmol/L), head computed tomography (CT) utilization, and central venous line (CVL) placements. A secondary goal of this study was to determine whether blood pressure was associated with treatment of cerebral edema. A *post hoc* analysis examined the incidence of hypokalemia (potassium <3 mmol/L).

Data Collection

SAP BusinessObjects (SAP, Walldorf, Germany), a business intelligence platform, was used to interrogate a cloned EHR database containing information from all patient encounters at our institution during the study period. Data were extracted in .xml format and organized for subsequent analysis using Microsoft Excel (Microsoft Corp., Redmond, WA USA). All patients >1 month of age admitted from April 2009, when the current study center campus opened, to May 2016 with a final International Classification of Diseases (ICD) 9 or 10 version diagnosis code consistent with DKA (ICD-9 codes 250.1x, 250.2x, 250.3x or ICD-10 E10.10 and E13.10) were included. Patients were considered to have DKA if a minimum pH less than 7.3 was identified during hospitalization. Minimum pH was used instead of initial pH for cohort identification to account for the downtrend in pH observed following initial resuscitation in some patients. Validation of this search strategy was

performed by randomly reviewing unstructured assessments in admission history documentation of 10% of the identified patients.

Details of patient care provided at outside hospitals or during transport are not recorded as structured elements in our EHR and were not included in this analysis. Demographic and clinical data included age, sex, Glasgow coma scale (GCS) score, pH and pCO₂ from arterial, venous and capillary blood gases, and serum concentrations of glucose, blood urea nitrogen (BUN), beta-hydroxybutyrate (BOHB), sodium (Na⁺), and chloride (Cl⁻). Missing data (less than 1% of retrieved data) was populated through investigator chart review. When applicable, arterial and capillary pH was adjusted to a venous scale by subtracting 0.05 and pCO₂ was converted by adding 6 mmHg. A correction factor of 1.6 mEq/L was added to Na⁺ for every 100 mg/dL increment of blood glucose above 100 mg/dL.(12) Head CT, mannitol and 3% aqueous saline utilization were assessed by searching for completed orders. Placement of CVLs were identified by searching nursing documentation for completed insertion site assessments. Systolic blood pressure (SBP) z scores were calculated based on age at time of admission and height z scores calculated using recorded height during the admission. Patient height during admission was occasionally carried forward from a previous clinic visit or prior admission. This risked biasing height z scores lower and inflating SBP z scores. Height z scores greater than 3 or less than -3 were therefore eliminated. The distribution of height z scores was then re-centered to zero by adding the median of the calculated distribution to each z score. A subset of inpatient height measurements was compared to outpatient follow-up heights to ensure accuracy (see supplemental materials). LOS was calculated as the difference of hospital admission time and discharge time, excluding time in the emergency department, and log-transformed due to high skew.

Data Analysis

For our primary analysis, linear and logistic regression were used to compare outcomes before and after the implementation of institutional performance improvement interventions. Interventions were considered in full effect in January 1, 2013. A sensitivity analysis was performed to determine whether an alternative intervention cut point significantly changed the measured outcomes. This included testing the intervention in April 2012 when the requirement for PICU admission was established, testing the intervention at the midpoint between the PICU admission requirement and hospital DKA guideline implementation (August 2012), and a final, conservative approach that tested the impact of excluding the cohort between April and December 2012. Regression models incorporated robust standard errors clustered by patient to account for intragroup correlation among patients with multiple encounters during the study period. The impact of time was considered both surrounding performance improvement interventions using a dichotomous *intervention* variable, as well as across the entire study period using a continuous *week* variable. Likelihood ratio tests for interaction were used to test whether trends in outcomes changed significantly before and after implementation of the intervention. Interaction terms with significant likelihood ratio tests ($P < 0.2$) were included in the final models.

Subgroup analyses examined outcomes in patients with severe DKA and established diagnoses of diabetes at the time of presentation. Severe DKA was defined as patients with a presenting pH less than 7.1. Patients with new-onset type 1 diabetes receive 2–3 days of diabetes management teaching following resolution of DKA, with the duration of education influenced by patient and family comfort and knowledge acquisition. To examine LOS in a population not subject to this teaching regimen, patients with established diabetes were distinguished from presentations of new-onset diabetes by searching all previous inpatient and outpatient encounters for ICD-9 or 10 codes consistent with a diagnosis of diabetes. This strategy isolated patients with known diabetes but did not separate the cohort into new-onset and previously diagnosed diabetes status, since the remaining patients might have received their routine diabetes care outside of our system and would not appear in our EHR database during the search.

A multivariable model for treated cerebral edema was constructed with backward stepwise logistic regression, incorporating clinical parameters that demonstrated significant association with treatment. For unadjusted analyses, the two-sample t test and Mann-Whitney test were used to examine parametric and nonparametric continuous variables, respectively. The chi-squared test was used for categorical variables. Alpha was set to 0.05 and all *P* values are two-tailed. Height and SBP z scores were calculated with *R* (www.r-project.org and R Studio Inc., Boston, MA, USA) using an open source function based on published standards for childhood height and blood pressure percentiles.(13–15) All other analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA).

Results

Searching ICD-9 and 10 codes for DKA retrieved 1379 patients from our EHR database, admitted between April 2009 and May 2016. Limiting this cohort to patients with a pH less than 7.3 during hospitalization yielded 1225 patients, of which 742 were identified as patients with known diabetes and 588 had BOHB sampled during admission. GCS scores were unavailable for one patient. One patient (0.08%) died. Patients in the post-intervention period were older, presented with a higher pCO₂, lower BUN and lower corrected Na⁺ values (Table 1).

The proportion of encounters with treated cerebral edema was 2.4% for the entire cohort, with 2.5% of pre-intervention encounters and 2.4% of post-intervention encounters receiving treatment, respectively (Table 2). The incidence of cerebral edema did not differ between patients less than 5 years of age (2/81, 2.47%) versus those 5 years of age or older (28/1144, 2.45%). Sensitivity analysis demonstrated that different intervention cut points did not significantly influence the directional change in outcomes before and after the intervention (Supplemental Table 1). Regression analysis did not demonstrate any change in the incidence of patient encounters treated for cerebral edema or developing hypoglycemia with relation to the intervention (Table 3). In multivariable analysis, the incidence of patient encounters developing severe hyperchloremia and undergoing head CT significantly decreased over the study period (Table 3). pH was independently associated with all outcomes of interest, with lower pH associated with increased odds of developing all outcomes except hypoglycemia. Table 4 displays the association between pH and outcomes

adjusted for the mean values of model covariates. The intervention was associated with a change in the slope of mean LOS for patients presenting with a pH less than 7.1, with a significant upward slope in the pre-intervention period changing to a significant downward slope in the post-intervention period (Supplemental Table 3). Figure 1 displays mean LOS (log-hours) for admissions of patients with known diabetes and severe DKA (n = 185). *Post hoc* multivariable analysis did not demonstrate any change in the incidence of hypokalemia over the study period or with relation to the intervention.

Data were available for 926 patients to calculate *z* scores of SBP. Backward stepwise regression identified lower presenting pH, pCO₂, and SBP *z* score, and a higher BUN to be significantly associated with treatment for cerebral edema during hospitalization (Table 5). A higher maximum SBP *z* score during hospitalization was significantly associated with treatment for cerebral edema, and remained significantly associated after adjustment for presenting pH, pCO₂, corrected Na⁺, BUN and presenting SBP *z* score (Odds Ratio 1.85 [95% confidence interval 1.37–2.52]; *P*<0.001). Figure 2 displays a boxplot of presenting and maximum SBP *z* scores stratified by treatment for cerebral edema. Maximum SBP occurred at a range of times relative to cerebral edema treatment, occurring more than 12 hours before or after treatment in 15 (50%) patients.

Discussion

In this study, we assessed outcome measures surrounding a performance improvement intervention related to DKA treatment in a large cohort (N = 1,225) of children with DKA. The intervention consisted of two system-level changes, (1) mandated PICU admission for all DKA patients requiring an insulin infusion and (2) implementation of an evidence-based DKA guideline with an accompanying order set. Using data collected directly from an EHR database, we demonstrate a decline in severe hyperchloremia and head CT utilization in patients with DKA over the entire study period and a reduction in variation of LOS following the intervention among patients with severe DKA at our institution. The proportion of patients treated for cerebral edema did not change in the post-intervention (2.4%) versus pre-intervention (2.5%) period. To the best of our knowledge, the present study also represents the largest reported cohort to date examining physical and biochemical risk factors for cerebral edema in children with DKA and is the first study to identify SBP as significantly associated with cerebral edema treatment.

Declining utilization of head CT in patients with DKA, irrespective of the performance improvement intervention, likely indicates increasing recognition that this diagnostic study does not frequently influence management and appreciation for the potentially detrimental effects of ionizing radiation in children.(16,17) The incidence of severe hyperchloremia decreased significantly over time and following the intervention. This change is likely multifactorial and related to guideline recommendations to use potassium phosphate or acetate instead of potassium chloride, as well as guidance for changing to 0.45% saline with the addition of dextrose in management.

The known relationship between hyperchloremia and LOS may be related to the significant declining trend in LOS observed in the post-intervention period.(18) Post-intervention LOS

confidence intervals narrowed suggesting a decrease in practice variability, improving the predictability of LOS at our institution, though this is also influenced by the larger number of patients in the post-intervention cohort compared to pre-intervention. Mandating admission to the ICU may have contributed to this reduced variation by limiting primary management to a smaller group of attending physicians, as opposed to primary decision-making occurring across both the non-ICU and ICU environments. Guideline implementation for DKA management has been shown to reduce LOS at other institutions. (3,19,20) Koves et al. demonstrated a reduction in PICU LOS following implementation of standardized DKA management, though there was an accompanying increase in PICU DKA admissions suggesting lower overall PICU DKA acuity. While both Al Nemri et al. and Martin et al. demonstrated reductions in LOS following pathway implementation, both studies examined smaller cohorts and post-intervention LOS in each study was longer than our institution's pre-intervention LOS. Pre-intervention, mean LOS for patients in the present cohort was comparable to the reported national mean LOS for DKA at 38 children's hospitals (2.8 versus 2.5 days).(21)

Our study intervention consisted of changes in DKA treatment predominantly influencing components of medical management such as fluid titration and response times to laboratory results. Socioeconomic characteristics such as poverty and type of insurance are also determinants of LOS in DKA.(22) Focusing on LOS for patients with established diabetes in the present study excluded the contribution of inpatient teaching time for new diagnoses, which is typically 2–3 days at our institution, but did not exclude other social and educational factors influencing LOS in the cohort. Educational resources for patients with known diabetes with DKA did not change substantially throughout the study period, reducing the likelihood of unaddressed confounding factors in the analysis.

This study demonstrates the utility of EHR-housed data to meet the needs of both performance improvement initiatives, as well as clinical investigations. Intersecting performance improvement initiatives with “query-able” EHR databases offers a facile method of tracking guideline adherence and refining clinical pathways without the need for time-intensive chart review. Data collected with this approach can provide objective thresholds for risk stratification to guide resource intensity. Lower pH and pCO₂ and higher BUN at presentation were independently associated with treatment for cerebral edema in this EHR-derived cohort, findings that are compatible with previous reports from both prospective and retrospective observational studies.(12,23–25) Hypertension has been previously described as a feature of DKA and frequently occurs despite intravascular volume depletion secondary to the osmotic diuresis that precedes presentation. In a study of 33 diabetic children in DKA, 82% were hypertensive during the first 6 hours of admission and more than 50% remained hypertensive at their second outpatient follow-up.(11) The physiologic mechanism of hypertension in DKA is not completely understood, though it may be related to excess catecholamines, increased circulating cortisol, pain and anxiety, or release of antidiuretic hormone secondary to hyperosmolality.(26–28)

Whether hypertension contributes to vasogenic cerebral edema in patients with DKA or serves as a protective response to preserve cerebral perfusion in the setting of elevated intracranial pressure is not known.(11) Profound dehydration in patients with severe DKA

may mitigate a compensatory hypertensive response and contribute to cerebral ischemia. Previous studies reporting elevations in markers of neuronal injury, blood-brain barrier breakdown, basal ganglia lactate and neuroinflammation indicate a possible contribution of cerebral hypoperfusion to the development of cerebral edema in DKA.(29–32) Lower presenting and higher maximum SBP in patients treated for cerebral edema compared to patients not treated suggests a time-dependent interplay between blood pressure and neurologic decompensation; however, timing of maximum blood pressure did not readily correlate with timing of cerebral edema treatment. Further study with detailed time-series analyses may help to better characterize the relationship between blood pressure and cerebral edema.

Our cohort's mean presenting SBP z score corresponds to approximately the 88th percentile of SBP for age, though patients treated for cerebral edema had a mean presenting blood pressure corresponding to the 72nd percentile. Conversely, mean maximum SBP corresponded to the 99.99th and 99.3rd percentiles for patients treated and not treated for cerebral edema, respectively. For a 13-year-old male of average height, these maximum SBP percentiles correspond to values of approximately 149 and 136 mmHg. While clinically subtle, 10 mmHg differences in blood pressure have proven clinically significant in other cerebral perfusion-dependent diseases such as stroke.(33)

A strength of this study is the large, EHR-derived cohort which allowed for the construction of a multivariable model for cerebral edema with sufficient degrees of freedom to incorporate both biochemical variables and SBP. That our model identified presenting pH, pCO₂ and BUN alongside SBP as significantly associated with cerebral edema strengthens the plausibility of our findings as these biochemical parameters have been previously associated with cerebral edema.(12) To the best of our knowledge this is the first study to examine this diverse array of outcomes surrounding implementation of a management guideline for DKA. Incorporating time as a continuous variable in regression models revealed trends not apparent in the unadjusted, before-after analysis. Accordingly, we avoided misattributing declines in patients developing severe hyperchloremia and CVL insertions to implementation of the guideline. Our reported mortality of 0.08% compares favorably to that reported for other large cohorts of children with DKA (0.03% to 0.18%).(12,34)

This study is limited by its retrospective design. Apparent severity of the cohort may have been reduced by exclusion of pre-hospital data in analysis, specifically at outside hospitals and during transport. Likewise, patients who received treatment for cerebral edema prior to arrival but not following admission were not counted as cerebral edema cases. Defining cerebral edema as receiving treatment with either mannitol or 3% aqueous saline may have introduced bias by excluding patients with clinically relevant cerebral edema who did not receive treatment. The prevalence of cerebral edema in the current study of 2.4% is higher than studies that have relied on billing codes to identify cerebral edema, but is comparable to studies that have relied on clinical documentation.(3,35) It is possible that the observed association between cerebral edema and pH, BUN and pCO₂ were driven by decisions to treat based on the known relationships between these parameters and cerebral edema.

However, we expect that patient's clinical status guided ultimate treatment decisions in most cases.

Conclusion

Using structured EHR data we have demonstrated that system-level changes in the management of DKA were associated with improved outcomes at our institution. Additionally, we replicated associations between presenting biochemical parameters and cerebral edema in the largest cohort to date and identified blood pressure as a potential harbinger of neurologic decompensation. Further study is warranted to better understand the relationship between blood pressure and cerebral edema in children with DKA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BOHB	beta-hydroxybutyrate
BUN	blood urea nitrogen
CT	computed tomography
CVL	central venous line
DKA	diabetic ketoacidosis
EHR	electronic health record
GCS	Glasgow coma scale
ICD	international classification of diseases
LOS	length of stay
Na⁺	sodium
Cl⁻	chloride
OR	Odds Ratio
PICU	pediatric intensive care unit
QI	quality improvement

SBP systolic blood pressure

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Figure 1.

Segmented regression displaying mean length of stay (Avg LOS) for admissions of patients with known diabetes mellitus (DM) presenting with an initial pH less than 7.1 ($n = 185$), before and after all performance improvement initiatives were in effect on December 31, 2012. Each point represents Avg LOS for three months. Slopes are significantly different ($P = 0.038$).

Figure 2.
Box plot of presenting and maximum SBP z scores according to whether treatment for cerebral edema was administered.

Table 1.

Presenting cohort characteristics, stratified by intervention and by treatment for cerebral edema

Characteristics	Entire Cohort		Pre-Intervention		Post-Intervention		Cerebral Edema Treatment		No Cerebral Edema Treatment		P
	N = 1225	Mean [95% CI]	n = 565	Mean [95% CI]	n = 660	Mean [95% CI]	n = 30	Mean [95% CI]	n = 1195	Mean [95% CI]	
Age (years)	12.2 [12.0 – 12.4]		11.8 [11.2–12.3]		12.6 [12.1–13.0]		12.3 [10.7–13.8]		12.2 [11.8–12.6]		0.93
Female, n (%)	656 (53.6)		301 (53.3)		355 (53.8)		15 (50)		641 (53.6)		0.69
pH	7.16 [7.15 – 7.17]		7.16 [7.15–7.17]		7.16 [7.15–7.17]		7.0 [7.0–7.0]		7.16 [7.16–7.17]		<0.001
BUN (mg/dL)	19 [19 – 20]		20 [19–21]		18 [18–19]		31 [23–38]		19 [18–20]		0.002
pCO ₂ (mmHg)	25 [25 – 26]		25 [24–25]		26 [25–26]		21 [18–24]		25 [25–26]		0.01
Corrected Na (mEq/L)	139 [139 – 139]		140 [140–141]		137 [137–137]		144 [141–148]		139 [138–139]		0.002
Glucose (mg/dL)	461 [449 – 473]		469 [449–490]		453 [436–471]		712 [588–836]		454 [442–467]		<0.001
	n = 926		n = 435		n = 491		n = 24		n = 902		
Max SBP z score *	2.52 [2.43 – 2.60]		2.46 [2.34–2.58]		2.57 [2.42–2.71]		3.75 [3.19–4.31]		2.48 [2.38–2.58]		<0.001
SBP z score	1.22 [1.13 – 1.30]		1.23 [1.11–1.37]		1.2 [1.06–1.33]		0.58 [–0.02–1.17]		1.23 [1.13–1.33]		0.03
	n = 1224		n = 565		n = 659		n = 30		n = 1194		
GCS score	14.7 [14.6 – 14.8]		14.7 [14.5–14.8]		14.7 [14.6–14.8]		12.2 [10.8–13.5]		14.7 [14.7–14.8]		<0.001
	n = 587				n = 587		n = 15		n = 572		
Beta-hydroxybutyrate (mmol/L)	7.9 [7.7 – 8.1]		--		7.9 [7.7–8.1]		9.8 [8.3–11.4]		7.8 [7.6–8.1]		0.01

* Represents maximum SBP z score during hospitalization

Table 2.

Unadjusted outcomes pre- and post-intervention

N	Pre-Intervention (Ends December 31, 2012)	Post-Intervention (Begins January 1, 2013)	P
	565	660	
Cerebral edema ^a	14 (2.5)	16 (2.4)	0.95
Head CT ^a	21 (3.7)	22 (3.3)	0.72
CVL ^a	49 (8.7)	31 (4.7)	0.005
Severe hyperchloremia (Cl >120 mEq/L) ^a	166 (29)	148 (22)	0.005
Hypoglycemia (blood glucose <70 mg/dL) ^a	59 (10)	72 (11)	0.79
Median LOS (hours) ^b	64.1 (40.0, 88.9)	56.5 (39.3, 87.3)	0.13
Mean Log LOS (log hours) ^c	1.762 (0.26)	1.744 (0.24)	0.20

^a n (%);^b median (interquartile range);^c mean (standard deviation)

Table 3.

Multivariable outcome models for all patients with DKA (n = 1,224)

Characteristic	Hypoglycemia (glucose <70 mg/dL)	Severe hyperchloremia (Cl ⁻ >120 mEq/L)	CVL placement	Head CT obtained	Cerebral edema treatment	Hospital LOS (log hours)
	OR	OR	OR	OR	OR	β
	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]
	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>
Intervention	0.9 [0.4 – 1.8] <i>0.73</i>	2.0 [1.0 – 4.1] <i>0.046</i>	1.1 [0.3 – 3.5] <i>0.88</i>	3.2 [1.2 – 8.3] <i>0.02</i>	1.2 [0.3 – 4.6] <i>0.75</i>	-0.026 [-0.077 – 0.026] <i>0.33</i>
Week	1.0 [1.0 – 1.0] <i>0.51</i>	0.996 [0.993 – 0.9997] <i>0.03</i>	1.0 [1.0 – 1.0] <i>0.12</i>	0.994 [0.989 – 0.999] <i>0.01</i>	1.0 [1.0 – 1.0] <i>1.0</i>	0 [0.000 – 0.000] <i>0.18</i>
Age (years)	1.0 [0.9 – 1.0] <i>0.61</i>	0.9 [0.9 – 0.9] <i><0.001</i>	1.0 [1.0 – 1.0] <i>0.58</i>	1.0 [0.9 – 1.0] <i>0.41</i>	1.0 [0.9 – 1.1] <i>0.94</i>	-0.016 [-0.019 – -0.013] <i><0.001</i>
Female sex	1.4 [0.9 – 2.1] <i>0.13</i>	1.4 [0.9 – 2.0] <i>0.10</i>	2.3 [1.3 – 3.8] <i>0.003</i>	1.2 [0.6 – 2.4] <i>0.64</i>	0.8 [0.4 – 1.6] <i>0.51</i>	-0.014 [-0.042 – 0.014] <i>0.34</i>
pH	7.4 [1.1 – 50.7] <i>0.04</i>	0.0005 [0.000 – 0.002] <i><0.001</i>	0.001 [0.000 – 0.015] <i><0.001</i>	0.01 [0.001 – 0.176] <i>0.002</i>	0.001 [0.000 – 0.044] <i>0.001</i>	-0.538 [-0.663 – -0.413] <i><0.001</i>
pCO ₂ (mmHg)	1.0 [0.9 – 1.0] <i>0.03</i>	0.9 [0.9 – 0.9] <i><0.001</i>	1.0 [1.0 – 1.0] <i>0.75</i>	1.0 [0.9 – 1.0] <i>0.26</i>	0.9 [0.9 – 1.0] <i>0.03</i>	-0.004 [-0.006 – -0.002] <i><0.001</i>
Corrected Na ⁺ (mEq/L)	1.0 [0.9 – 1.0] <i>0.48</i>	1.2 [1.2 – 1.3] <i><0.001</i>	1.1 [1.0 – 1.1] <i>0.002</i>	1.0 [1.0 – 1.1] <i>0.67</i>	1.0 [1.0 – 1.1] <i>0.52</i>	0.004 [0.001 – 0.007] <i>0.003</i>
GCS score	0.8 [0.7 – 0.9] <i>0.001</i>	0.9 [0.8 – 1.1] <i>0.38</i>	0.7 [0.6 – 0.8] <i><0.001</i>	0.8 [0.7 – 1.0] <i>0.01</i>	0.9 [0.8 – 1.0] <i>0.02</i>	-0.01 [-0.022 – 0.002] <i>0.10</i>
Glucose (mg/dL)	1.0 [1.0 – 1.0] <i>0.93</i>	1.001 [1.000 – 1.002] <i>0.01</i>	1.0 [1.0 – 1.0] <i>0.08</i>	1.0 [1.0 – 1.0] <i>0.80</i>	1.0 [1.0 – 1.0] <i>0.07</i>	0.0002 [0.0001 – 0.0002] <i><0.001</i>
BUN (mg/dL)	1.0 [1.0 – 1.0]	1.0 [1.0 – 1.0]	1.0 [1.0 – 1.0]	1.0 [1.0 – 1.1]	1.0 [1.0 – 1.1]	-0.002 [-0.004 – -0.001]

	Hypoglycemia (glucose <70 mg/dL)	Severe hyperchloremia (Cl ⁻ >120 mEq/L)	CVL placement	Head CT obtained	Cerebral edema treatment	Hospital LOS (log hours)
	OR	OR	OR	OR	OR	β
Characteristic	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]
	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>
	0.14	0.74	0.08	0.08	0.01	0.01

All characteristics represent values at presentation to the study hospital

Table 4.

Association between adjusted pH and outcomes

	Hypoglycemia (glucose <70 mg/dL)	Severe hyperchloremia (Cl ⁻ >120 mEq/L)	CVL placement	Head CT obtained	Cerebral edema treatment	Hospital LOS
	OR	OR	OR	OR	OR	Difference (hours)
	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]	[95% CI]
25 th versus 75 th percentile of presenting pH	0.71 [0.51 – 0.99]	3.67 [2.78 – 4.84]	3.06 [2.05 – 4.58]	2.17 [1.34 – 3.52]	3.39 [3.39 – 6.74]	11.8 [11.6 – 12.0]

Adjusted for intervention, week (a continuous variable modeling time for the duration of the study period), pCO₂, blood urea nitrogen, Glasgow coma scale score, corrected sodium, glucose, age and sex at presentation.

Table 5.

Multivariable model of presenting characteristics associated with cerebral edema

	OR [95% CI]	<i>P</i>
	n = 926	
pH	0.0001 [0.000–0.004]	<i><0.001</i>
pCO ₂ (mmHg)	0.92 [0.86–0.99]	<i>0.02</i>
Corrected Na ⁺ (mEq/L)	1.08 [0.99–1.17]	<i>0.08</i>
BUN (mg/dL)	1.05 [1.02–1.09]	<i>0.006</i>
Initial SBP z score	0.77 [0.60–0.98]	<i>0.04</i>