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Hypertension During Diabetic Ketoacidosis in Children

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Abstract

OBJECTIVES: To characterize hemodynamic alterations occurring during diabetic ketoacidosis (DKA) in a large cohort of children and to identify clinical and biochemical factors associated with hypertension.

Study design: This was a planned secondary analysis of data from the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Study, a randomized clinical trial of fluid resuscitation protocols for children in DKA. Hemodynamic data (heart rate, blood pressure) from children with DKA were assessed in comparison with normal values for age and sex. Multivariable statistical modeling was used to explore clinical and laboratory predictors of hypertension.

RESULTS: Among 1258 DKA episodes, hypertension was documented at presentation in 154 (12.2%) and developed during DKA treatment in an additional 196 (15.6%), resulting in a total of 350 DKA episodes (27.8%) in which hypertension occurred at some time. Factors associated with hypertension at presentation included more severe acidosis, (lower pH and lower PCO_2), and stage 2 or 3 Acute Kidney Injury (AKI). More severe acidosis and lower Glasgow Coma Scale (GCS) scores were associated with hypertension occurring at any time during DKA treatment.

CONCLUSIONS: Despite dehydration, hypertension occurs in a substantial number of children with DKA. Factors associated with hypertension include greater severity of acidosis, lower PCO$_2$ and lower GCS scores during DKA treatment, suggesting that hypertension might be centrally mediated.

Diabetic ketoacidosis (DKA) is characterized by hyperglycemia, acidosis, and dehydration. During DKA, fluid losses resulting from osmotic diuresis, vomiting and hyperventilation lead to hypovolemia, although its degree does not correlate well with either patients' clinical characteristics or laboratory findings (1). The expected hemodynamic response to hypovolemia is tachycardia and hypotension. However, children with severe DKA have been reported to have hypertension (2, 3). In previous reports, hypertension was observed in children both at presentation and during treatment. The pathophysiology of this paradoxical hypertension is not understood. Both subtle and more severe cerebral injuries can occur in children with DKA (4–9) and several studies document abnormalities in cerebral blood flow during DKA (10–12). It is possible that hypertension in children with DKA might reflect neurophysiological changes resulting from altered brainstem perfusion (11).

The Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Study was a large randomized clinical trial of fluid resuscitation protocols for children with DKA (13). Children were randomized to one of four treatment arms to investigate the effects of fluid treatment variations on neurologic and neurocognitive outcomes. Data from frequent measurements of heart rate and blood pressure available for patients enrolled in the PECARN FLUID Study provided an opportunity to describe hemodynamic changes in children with DKA. In the current study, we present a detailed analysis of hemodynamic data in this large cohort of children with DKA. We describe heart rate and blood pressure measurements in these children and document clinical and laboratory findings associated with hypertension to provide insights into the cause of abnormal hemodynamics during DKA.

Methods.

This was a planned secondary analysis of data from a 13-center, 2×2 factorial design randomized controlled trial conducted at 13 emergency departments (EDs) in PECARN from 2011–16. Patients enrolled in the trial were randomized to one of four treatment arms that varied in regard to intravenous fluid infusion rate (more rapid versus slower rehydration) and fluid sodium content (0.9% NaCl versus 0.45% NaCl) (13, 14). A total of 1389 patients were randomized between February 2011 and September 2016. The Consolidated Standards of Reporting Trials flow chart for the primary outcome of the PECARN FLUID Study is provided in the appendix (Figure 1; available at www.jpeds.com). Detailed inclusion and exclusion criteria were published previously (13, 14). The main exclusion criteria included conditions unrelated to DKA that affect mental status or cognitive abilities, or substantial treatment for DKA prior to transfer to the study center. The study methods and primary trial results are presented in detail elsewhere (13, 14). Additional methods specific to the current analysis are described below.

All patient encounters included in the PECARN FLUID Study were eligible for inclusion in this analysis. Encounters were excluded if they were missing measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) or heart rate (HR) prior to DKA treatment initiation, or if there were fewer than three blood pressure (BP) measurements within the first six hours of treatment.

Measures.

Hemodynamic measurements were standardized for age and sex by calculating z-scores that indicate the number of standard deviations (SD) above or below the mean for the patient's age and sex (15,16). SBP and DBP were also standardized for height. In cases where height was unknown (n=28), average height (50th percentile for age and sex) was assumed. Hypertension was defined by an SBP z-score above 2 (i.e. greater than 2 SD above the age-, sex- and height-adjusted mean). Hypertension at presentation was defined as both the initial SBP z-score and another SBP z-score within 2 hours of the initial measurement greater than 2. Hypertension during DKA was defined as two or more SBP z-scores above 2 within any two-hour interval during DKA treatment. Hypotension at presentation was defined as an initial SBP z-score of −2 or lower followed by another SBP z-score less than −2 within two-hours. Hypotension during DKA treatment was defined as 2 or more SBP measurements with z scores −2 or lower within any two-hour interval during DKA treatment.

The area under the curve (AUC) and duration of hypertension were calculated using the trapezoidal method (17). AUC was defined as the area (in minute-standard units) of the curve more than 2 SD above the age-, sex- and height-adjusted mean SBP. Additionally, SBP and DBP z-scores were used to calculate mean arterial pressure (MAP) z-scores. MAP calculations required standard age-, sex-, and height-specific means and variances (15,16), and the covariance between SBP and DBP estimated from the dataset. Sensitivity outcomes of hypertension at presentation based on MAP and hypertension during DKA based on MAP were calculated using the same methods as SBP-based hypertension outcomes.

In addition to BP and HR measurements at presentation and during DKA treatment, we also recorded demographic information, biochemical data at presentation, the presence or absence of acute kidney injury (AKI) during DKA, and the occurrence of abnormal mental status during DKA. Serum creatinine measurements during DKA were used to determine the presence and severity of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group criteria (18)). The presence and severity of mental status abnormalities during DKA were determined by evaluation of Glasgow Coma Scale (GCS) scores that were measured hourly for all study participants. Clinically overt cerebral injury was defined as a deterioration in neurologic status leading to hyperosmolar therapy or endotracheal intubation or resulting in death (13). All episodes of clinically apparent cerebral injury were reviewed by an independent adjudication committee to ensure that the episodes met diagnostic criteria (19) Patients were categorized in age groups (1–4, 5–9, 10–14 and 15–18 years), rounded to the previous whole number. Sodium concentrations were corrected for glucose by adding $0.016 \times$ (glucose −100 mg/dL), using glucose concentrations measured within 30 minutes of the sodium concentrations (20). Patients were

weighed at presentation and at discharge, and percent dehydration was calculated as the difference between the discharge and admission weight divided by the discharge weight.

Statistical Analyses.

We used means, standard deviations, and histograms to describe the distributions of peak and baseline standardized SBP, DBP, HR, and MAP values. We described the relationships between vital signs using Pearson Correlation Coefficients (r). We described demographic and clinical characteristics of hypertensive and non-hypertensive patients using means, standard deviations, counts and percentages. We also described the prevalence of hypotension in patients at presentation and during DKA treatment.

We used univariable and multivariable logistic regression models to explore associations between hypertension and demographic, clinical, and biochemical factors. The logistic model for hypertension at presentation included age, baseline laboratory measures, a baseline measure of AKI, and baseline GCS score as covariates. The logistic model for hypertension at any time during DKA included age, baseline laboratory measures, AKI at any time, the lowest measured GCS score, and study treatment arm assignment. Treatment arms varied only in rate of intravenous fluid infusion and fluid sodium content (13). Other aspects of DKA treatment were consistent among study arms. Due to the substantial number of patients with AUCs of zero (i.e. no SBP more than 2 SD above the age-, sex- and height-adjusted mean), we used a zero-inflated negative binomial model to explore the relationship between covariates and AUC. This two-part model fit a logistic regression component to estimate the likelihood of hypertension. A separate negative binomial regression component estimated the effects of age, baseline laboratory measures, AKI at any time, the lowest measured GCS score, and study treatment arm assignment on the magnitude of the AUC among those who developed hypertension. All covariates included in the univariable models were included in multivariable models with the exception of variables missing for >10% of patients. In sensitivity analyses, we fit logistic models to MAP-based hypertension outcomes. Variance inflation factors were calculated to evaluate the effect of collinearity. Statistical analyses were performed using SAS Software (version 9.4).

Results.

During the enrollment period, 2848 children with DKA were eligible for the PECARN FLUID Study, (13) and 1389 of these were randomized/enrolled. Lack of enrollment was either due to unwillingness to consent (n=812) or lack of study personnel to enroll the patient (n=631). 1258 patients (90.6%) had sufficient hemodynamic data during treatment for inclusion in the current analyses (Figure 1). Patients were excluded due to lack of adequate documentation of vital signs prior to treatment (n=93) or lack of sufficient SBP measurements (3 or more) recorded in the first 6 hours of DKA treatment (n=38).

The distributions of SBP, DBP, MAP and HR z-scores for the study patients, including values at presentation and peak values during DKA treatment, are provided in Figure 2. As expected, most patients presented with elevated HRs; on average, HRs at presentation were 3 SD above age- and sex-adjusted normal values. At their peak, HRs were almost 4 SD above age- and sex-adjusted normal values.

The distribution of BP measurements at presentation demonstrated elevation in comparison with normal values based on age, height and sex. At presentation, average SBP, DBP and MAP values were approximately 1 SD above age-, height- and sex-adjusted normal values. BP values increased during DKA treatment such that peak values were approximately 2 SD above age-, height- and sex-adjusted normal values. There was a modest correlation between SBP and DBP measurements (r=0.55 at presentation, r=0.59 peak). HR and SBP were somewhat correlated (r=0.20 at presentation, r=0.35 peak). Heart rate and DBP were not correlated at presentation (r=0.03), and peak values were only somewhat correlated (r=0.18).

Hypertension was documented at presentation in 154 of 1258 of DKA episodes (12.2%, Table 1). Hypertension resolved rapidly (under 2 hours) in 36 episodes (2.9%) and persisted for 2 hours or more in 118 episodes (9.4%). In an additional 196 episodes (15.6%) blood pressure was normal at presentation but hypertension developed later during DKA treatment. The overall rate of hypertension (at any time during DKA) was 27.8% (350/1258) (Table 1). Among the 196 patients who developed hypertension after presentation, the median time to hypertension was 2.9 hours after the initial vital signs were taken (Interquartile range: 1.2–5.0 hours). Among the 350 DKA episodes with hypertension, median duration was 4.0 hours (Interquartile range: 2.2–7.7 hours). DKA episodes with and without hypertension (either at presentation or at any time during DKA) were similar with respect to ethnicity, sex, diagnosis of new-onset of diabetes, and fluid treatment protocol to which they were assigned in the original study. Black or African American patients were more likely to have hypertension at any time but were not more likely to have hypertension at presentation.

A small number of patients (n=12) developed clinically overt cerebral injury. In the univariable analysis, these patients were significantly more likely to develop hypertension during treatment (Table I) but were not significantly more likely to present with hypertension.

Model results for hypertension at presentation are shown in Table 2. In both the univariable comparisons and multivariable models, hypertension at presentation was associated with more severe acidosis (lower pH, and lower pCO_2) and stage 2 or 3 AKI. Lower glucose and glucose-corrected sodium concentrations at presentation were also associated with hypertension at presentation in the multivariable model. Lower baseline serum bicarbonate concentrations and lower GCS scores at presentation were associated with hypertension at presentation in univariable comparisons but these associations were no longer significant in the multivariable model.

Model results for development of hypertension any time during DKA are shown in Table 3. More severe acidosis (lower pH) and lower GCS scores were associated with hypertension during DKA in both univariable comparisons and in the multivariable model. AKI as well as lower pCO_2, lower baseline serum bicarbonate, higher baseline glucose and higher baseline glucose-corrected sodium concentrations were associated with hypertension during DKA treatment in univariable comparisons but not in the multivariable model.

In sub-analyses, we used calculated mean arterial pressure (MAP) z-scores in place of SBP as the indicator of hypertension. 7% of children presented with MAP z-scores more 2 SD

above the mean for age, sex and height, and an additional 10% developed high MAP during DKA treatment. Factors associated with hypertension defined by MAP were similar to those for hypertension defined by SBP with the exception of younger age which was more strongly associated with hypertension defined by MAP than with hypertension defined by SBP (Table 4 and Table 5; available at www.jpeds.com).

Model results for hypertension severity (AUC for SBP z-scores) are provided in Table 6 (available at www.jpeds.com). More severe acidosis (lower pH and lower pCO_2) and stage 2 AKI were associated with more severe hypertension in both univariable comparisons and in the multivariable model. Younger age was also associated with severe hypertension in the multivariable model. Lower baseline serum bicarbonate, lower percentage dehydration, AKI, and lower GCS scores were associated with more severe hypertension in univariable comparisons but not in the multivariable model.

There were no associations between hypertension and fluid treatment arm assignment in any of the analyses. Hypotension was noted in 2 patients (0.2%) at presentation. An additional 40 patients (3.3%) developed hypotension during treatment. Two patients who presented with hypertension later developed hypotension during DKA treatment.

Discussion.

Despite dehydration, many children with DKA present with hypertension or develop hypertension during treatment. In this study, we documented an association between hypertension and more severe acidosis and hypocapnia (pH and pCO_2). Furthermore, we found that hypertension during DKA treatment was associated with alterations in mental status, even after adjusting for factors reflecting DKA severity. Although the number of patients with clinically overt cerebral injury in the study (~1%) was small, precluding meaningful analysis, the frequency of clinically overt cerebral injury in hypertensive patients was higher than in patients without hypertension. Hypertension at presentation was not significantly associated with GCS abnormalities in multivariable models, however, this may have reflected delayed manifestation of mental status abnormalities or exclusion of patients presenting with very low GCS scores (<12) from the original study.

Hypertension during DKA is paradoxical and the etiology is unclear. The expected response to hypovolemia is tachycardia and hypotension. Although most patients in the study had elevated heart rates, hypotension was rare. Furthermore, there were no associations between hypertension and fluid infusion rate or fluid sodium content. Therefore, the role of intravascular volume in modulation of blood pressure during pediatric DKA appears to be atypical. Paradoxical hypertension in children with hypovolemia caused by other conditions has been documented previously in a case series that included a report of one child who was anephric (21). The authors hypothesized that the renin angiotensin system was unlikely to be involved but rather that hypertension in these cases might be caused by the action of elevated ADH levels on V1 receptors in blood vessels, in combination with a heightened adrenergic state. Furthermore, the authors noted that central perfusion in these patients might be dependent on very high peripheral resistance, resulting in systemic hypertension (21).

Several studies have documented abnormal elevations in cerebral blood flow during DKA treatment (10, 22). These alterations have been hypothesized to reflect hyperemia resulting from hypoperfusion/reperfusion. Furthermore, hypocapnia has been proposed as a factor responsible for cerebral hypoperfusion prior to DKA treatment (22). In our analyses, in addition to hypocapnia, lower glucose and sodium concentrations were also associated with hypertension at presentation. These factors are important determinants of intravascular volume during DKA, with elevated glucose and sodium concentrations resulting in relative preservation of intravascular volume among patients with higher serum osmolality. The association of lower glucose and sodium concentrations with hypertension at presentation again suggests that cerebral hypoperfusion prior to DKA treatment may be involved.

Furthermore, members of our group documented findings suggesting regional differences in cerebral blood flow during DKA treatment (11). Magnetic resonance imaging findings in the occipital cortex and medulla suggest possible hypoperfusion in these regions, in spite of hyperemia in the frontal cortex and other regions supplied by the anterior cerebral circulation (11). It is possible that decreased perfusion to the brainstem during DKA treatment interferes with normal autoregulatory mechanisms, resulting in hypertension. In an animal model, brainstem pO_2 levels were lower in hypertensive rats than in normotensive rats (23). These changes were associated with higher ambient adenosine triphosphate (ATP) and lactate concentrations and increases in BP. Higher levels of ambient ATP and lactate within the presympathetic circuits were hypothesized to lead to increased central sympathetic drive and concomitant increases in BP. Notably, children with life-threatening cerebral injury during DKA often manifest severe hypertension at the time of diagnosis of cerebral injury, followed by hypotension and abrupt declines in mental status (19). These findings raise the possibility that alterations in regional cerebral blood flow might also play a role in causing severe DKA-related brain injuries. Alternatively, hypertension might develop as a response to increased intracranial pressure during DKA (24). Several studies have documented vasogenic cerebral edema with decreased size of the cerebral ventricles during DKA (9, 21). Hypertension might reflect regulatory responses that maintain normal cerebral perfusion pressure in the setting of cerebral edema. Whether reflecting brainstem perfusion or intracranial pressure, a physiological connection between intracranial pathology and hypertension would explain associations between altered mental status during DKA and hypertension.

Hypertension was also associated with AKI during DKA, raising the possibility that renal injury might be involved in causing hypertension. Hypertension associated with renal disease may occur as a result of inappropriate sodium and fluid retention (25–27) or as a result of elevated angiotensin II levels (28). The former mechanism seems unlikely to be involved in causing hypertension during DKA because children with DKA are typically dehydrated, undergoing osmotic diuresis, and appropriately retaining sodium in response to volume depletion. We cannot exclude involvement of the latter mechanism, although, as previously noted, a report of paradoxical hypertension in a hypovolemic anephric child makes this mechanism less likely.(21) Alternatively, associations between AKI and hypertension during DKA may reflect the frequent co-occurrence of cerebral and renal injury in children with DKA such that the individual associations of these organ injuries are difficult to distinguish (29).

Our data highlight several important issues about monitoring of children with DKA. First, blood pressure regulation during DKA appears to be influenced by factors other than intravascular volume, and blood pressure measurements therefore should not be relied upon in decision making about fluid administration. Instead, other factors such as heart rate, clinical assessments of peripheral perfusion, trends in laboratory indicators of circulatory volume (BUN and hematocrit) and careful monitoring of fluid intake and output should be used to guide treatment decisions. Furthermore, possible associations between hypertension and intracranial pathology imply that children with hypertension should be monitored more closely for development of altered mental status and other signs of cerebral injury.

The current study has several limitations. Procedures for obtaining blood pressure measurements were not standardized across centers or between different care sites (emergency department, critical care unit or ward) at each study center. This may have caused some variability or errors in measurements. We suspect, however, that errors in measurements were infrequent as all participating centers were tertiary care children's hospitals with rigorous nursing standards. Furthermore, statistical analyses were stratified by center. Due to the low frequency of clinically overt cerebral injury during DKA, declines in GCS scores were the primary neurological outcome. Whether more modest declines in GCS scores result from processes similar to those causing more severe, clinically overt cerebral injury is unclear. However, studies suggest that GCS changes during DKA are associated with sub-clinical cerebral edema measured by MRI (30). In addition, patients with GCS scores <12 were excluded after the first two years of the parent study, reducing the proportion of patients with severely altered mental status at presentation. The frequencies of hypertension detected among children with DKA may have been higher if these patients had been included. In addition, children were excluded if treating physicians felt that a specific treatment regimen was needed (6% of eligible patients). It is possible that some more severely ill children were included in this group, and these children may have had a higher likelihood of either hypotension or hypertension. As this group was small, however, the effect of excluding these patients on the overall frequencies of hypotension and hypertension was limited. Finally, although BP was recorded throughout DKA treatment for all patients in this analysis, the frequency of measurements varied among study sites and there was no formal protocol to verify abnormal BP measurements. Our current data may therefore underestimate the frequency of hypertension during DKA.

In conclusion, hypertension is frequent in children with DKA, in spite of intravascular volume depletion. Acidosis and hypocapnia are significantly associated with hypertension in these children. The development of hypertension during DKA treatment and the association of hypertension with altered mental status suggests that a central mechanism may be involved in causing abnormal hemodynamic regulation. Further investigation of regional cerebral blood flow abnormalities during DKA is necessary to better understand these relationships and how these relate to life-threatening cerebral injuries in some children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

DKA	diabetic ketoacidosis
PECARN	Pediatric Emergency Care Applied Research Network
ED	Emergency Department
GCS	Glasgow Coma Scale
AKI	acute kidney injury
KDIGO	Kidney Disease Improving Global Outcomes
HR	heart rate
BP	blood pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
MAP	mean arterial pressure

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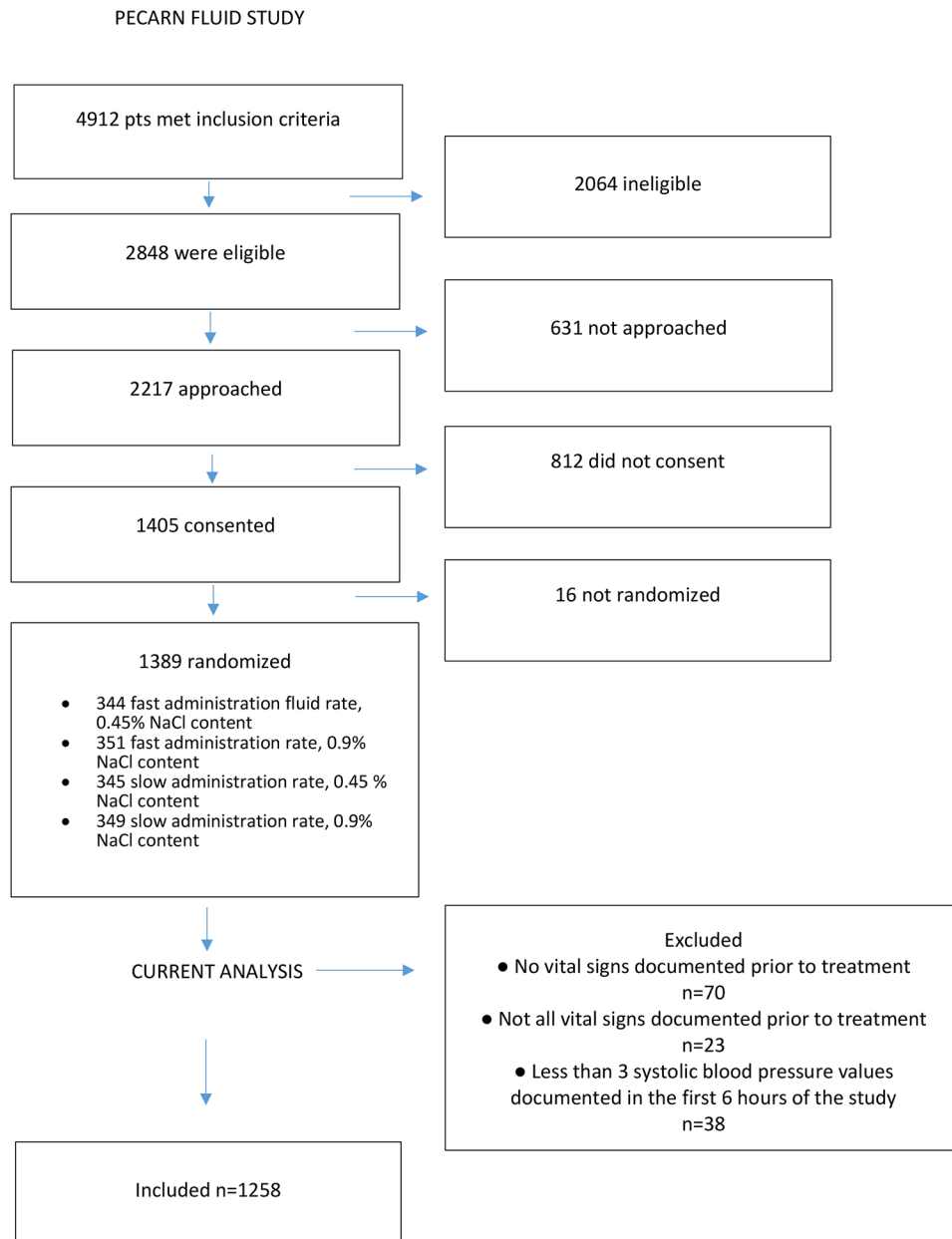
PECARN FLUID STUDY

Figure 1.
Patient Inclusion in the PECARN FLUID Study and Current Analysis.
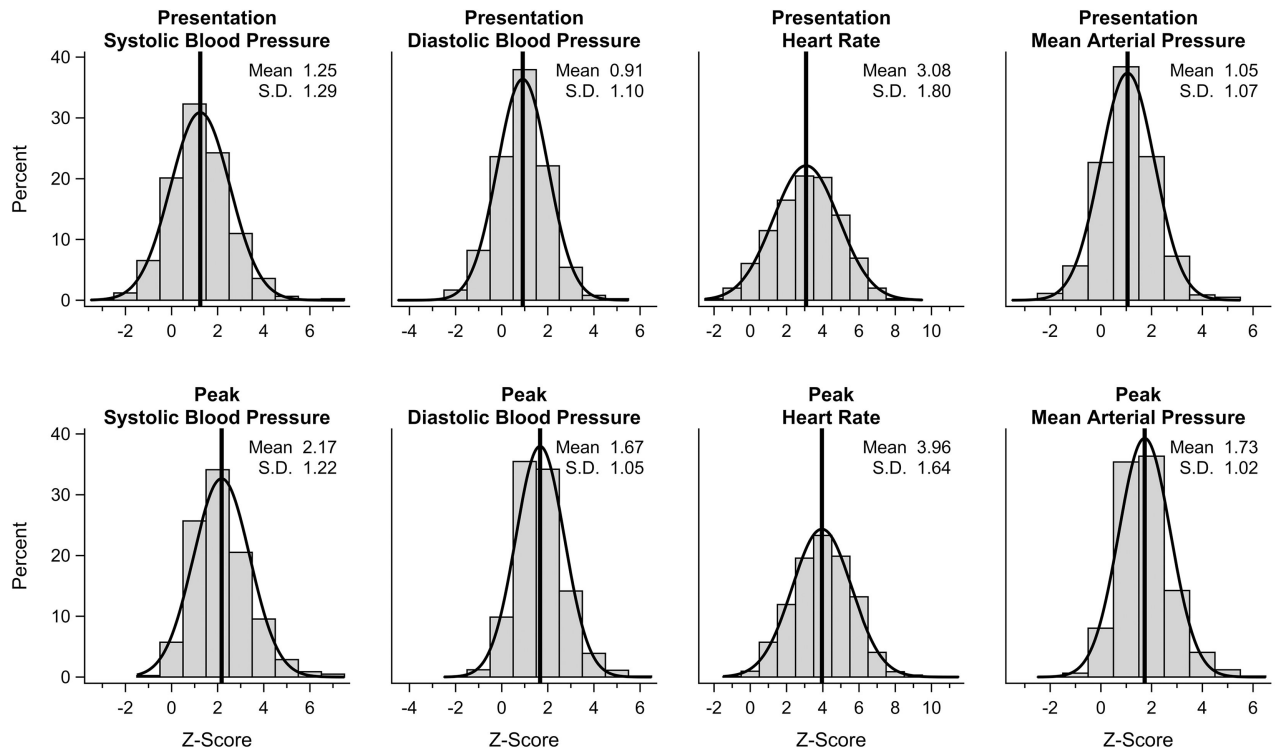
Figure 2.
Distribution of blood pressure and heart rate z-scores.

Table 1.

Characteristics of patients with and without hypertension.[*]

Characteristic	Hypertensive at presentation		Hypertensive at any time during DKA	
	No (N = 1104)	Yes (N = 154)	No (N = 908)	Yes (N = 350)
Mean Age, years (SD)	11.6 (4.0)	12.1 (4.1)	11.7 (3.9)	11.5 (4.5)
Race‡				
American Indian or Alaska Native	8 (1%)	0 (0%)	8 (1%)	0 (0%)
Asian	4 (0%)	0 (0%)	3 (0%)	1 (0%)
Black or African American	226 (20%)	39 (25%)	171 (19%)	94 (27%)
Native Hawaiian or Other Pacific Islander	6 (1%)	0 (0%)	5 (1%)	1 (0%)
White	760 (69%)	105 (68%)	642 (71%)	223 (64%)
Multiracial	40 (4%)	6 (4%)	34 (4%)	12 (3%)
Unknown	60 (5%)	4 (3%)	45 (5%)	19 (5%)
Ethnicity				
Hispanic or Latino	178 (16%)	25 (16%)	145 (16%)	58 (17%)
Not Hispanic or Latino	883 (80%)	124 (81%)	727 (80%)	280 (80%)
Unknown	43 (4%)	5 (3%)	36 (4%)	12 (3%)
Male	525 (48%)	70 (45%)	436 (48%)	159 (45%)
Previously diagnosed with diabetes	587 (53%)	84 (55%)	482 (53%)	189 (54%)
Percentage dehydration (SD) [†§]	5.3 (3.9)	6.0 (4.1)	5.2 (3.9)	5.7 (4.0)
Clinically overt cerebral injury during hospitalization‡	9 (0.8%)	3 (1.9%)	4 (0.4%)	8 (2.3%)
Treatment assigned in parent study				
A1: Fast 0.45% NaCl	273 (25%)	40 (26%)	224 (25%)	89 (25%)
A2: Fast 0.9% NaCl	289 (26%)	34 (22%)	246 (27%)	77 (22%)
B1: Slow 0.45% NaCl	270 (24%)	37 (24%)	214 (24%)	93 (27%)
B2: Slow 0.9% NaCl	272 (25%)	43 (28%)	224 (25%)	91 (26%)

[*] Hypertension based on SBP; Characteristics compared using Wilcoxon Rank-Sum Tests (dehydration) and Chi-Square Tests (all others).

[†] P-value <0.05 comparing Hypertension at Presentation. Percentage dehydration: p=0.04; All other tests of differences between hypertension at presentation groups were not significant: p 0.05

[‡] P-value <0.05 comparing Hypertension during DKA. Race: p=0.04; clinically overt cerebral injury during hospitalization: p=0.003; All other tests of differences between hypertension during DKA groups were not significant: p 0.05

[§] Missing dehydration data for 235 (19%): 158(17%) Not Hypertensive, 77(22%) Hypertensive

Table 2:

Factors Associated with Hypertension at Presentation: Univariable and Multivariable Logistic Regression Models

	Not Hypertensive at Presentation (N = 1104)	Hypertensive at Presentation (N = 154)	Univariable Odds-Ratio (95% CI)	Multivariable Odds-Ratio (95% CI)
Age Category				
0–4 years	99 (9.0%)	10 (6.5%)	0.62 (0.30, 1.30)	0.90 (0.38, 2.12)
5–9 years	239 (21.6%)	32 (20.8%)	0.82 (0.49, 1.35)	1.03 (0.57, 1.85)
10–14 years	524 (47.5%)	70 (45.5%)	0.83 (0.54, 1.26)	0.93 (0.57, 1.51)
15–18 years	242 (21.9%)	42 (27.3%)	Reference	Reference
Baseline pH	**7.17 (0.096)**	**7.08 (0.119)**	**0.44 (0.37, 0.53)**	**0.47 (0.36, 0.62)**
Baseline pCO$_2$ (mmHg)	**26.4 (7.40)**	**23.7 (7.11)**	**0.94 (0.91, 0.96)**	**0.96 (0.92, 1.00)**
Baseline BUN (mg/dL)	17.4 (8.01)	16.4 (6.57)	0.98 (0.96, 1.01)	0.98 (0.94, 1.01)
Baseline bicarbonate (mEq/L)	9.1 (3.23)	6.9 (2.50)	**0.76 (0.70, 0.81)**	0.98 (0.88, 1.11)
Baseline glucose (mg/dL)	**526.1 (158.08)**	**507.3 (162.00)**	0.92 (0.82, 1.04)	**0.84 (0.72, 0.98)**
Baseline sodium (mEq/L)	134.1 (5.21)	134.2 (4.92)	1.01 (0.97, 1.04)	***
Baseline glucose-corrected sodium (mEq/L)	**140.9 (5.24)**	**140.7 (5.13)**	0.99 (0.96, 1.03)	**0.95 (0.91, 1.00)**
Percentage Dehydration (SD)	5.3 (3.88)	6.0 (4.05)	1.04 (0.99, 1.09)	***
Acute Kidney Injury (AKI) at presentation				
No AKI	587 (53.2%)	69 (44.8%)	Reference	Reference
Stage 1	249 (22.6%)	39 (25.3%)	1.51 (0.97, 2.34)	1.63 (0.95, 2.78)
Stage 2	**155 (14.0%)**	**31 (20.1%)**	**2.24 (1.32, 3.79)**	**2.40 (1.15, 4.99)**
Stage 3	**22 (2.0%)**	**6 (3.9%)**	**3.23 (1.18, 8.87)**	**4.65 (1.11, 19.38)**
GCS at presentation				
<14	23 (2.1%)	9 (5.8%)	**3.26 (1.44, 7.38)**	1.26 (0.47, 3.34)
14	81 (7.3%)	21 (13.6%)	**2.08 (1.23, 3.52)**	1.11 (0.58, 2.12)
15	1000 (90.6%)	124 (80.5%)	Reference	Reference

Hypertension based on SBP

Reported values show mean (SD) or number of patients (percent of sample)

The odds-ratio for pH is the estimated multiplicative difference in odds for a 0.1 unit increase in pH; the odds-ratio for glucose is the estimated multiplicative difference for a 100 unit increase in glucose; all other odds ratios are the estimated multiplicative difference for a 1 unit increase (labs) or compared to the reference group.

Models adjusted for clinical site (not shown).

*** Sodium was not included in the multivariable model due to strong correlation with glucose-adjusted sodium. Dehydration was not included in the multivariable model due to 235 (19%) missing values.

Table 3:

Factors Associated with Hypertension Occurring at any Time During DKA Treatment: Univariable and Multivariable Regression Models

	Not Hypertensive During DKA (N = 908)	Hypertensive at Some Time During DKA (N = 350)	Univariable Odds-Ratio (95% CI)	Multivariable Odds-Ratio (95% CI)
Age Category				
0–4 years	69 (7.6%)	40 (11.4%)	1.41 (0.88, 2.28)	1.64 (0.90, 2.96)
5–9 years	201 (22.1%)	70 (20.0%)	0.84 (0.57, 1.22)	0.97 (0.61, 1.54)
10–14 years	443 (48.8%)	151 (43.1%)	0.81 (0.59, 1.11)	0.97 (0.66, 1.42)
15–18 years	195 (21.5%)	89 (25.4%)	Reference	Reference
Baseline pH	**7.18 (0.088)**	**7.10 (0.119)**	**0.46 (0.40, 0.53)**	**0.59 (0.47, 0.75)**
Baseline pCO$_2$ (mmHg)	26.7 (7.30)	24.3 (7.46)	**0.94 (0.92, 0.96)**	0.97 (0.94, 1.00)
Baseline BUN (mg/dL)	17.1 (7.46)	17.6 (8.74)	1.00 (0.99, 1.02)	0.99 (0.97, 1.02)
Baseline bicarbonate (mEq/L)	9.5 (3.18)	7.3 (2.79)	**0.77 (0.73, 0.81)**	0.93 (0.85, 1.01)
Baseline glucose (mg/dL)	517.3 (154.52)	540.7 (167.83)	**1.11 (1.02, 1.20)**	0.98 (0.88, 1.10)
Baseline sodium (mEq/L)	133.9 (5.11)	134.5 (5.31)	1.02 (0.99, 1.04)	***
Baseline glucose-corrected sodium (mEq/L)	140.6 (5.00)	141.6 (5.71)	**1.03 (1.01, 1.06)**	1.00 (0.97, 1.04)
Percentage dehydration (SD)	5.2 (3.87)	5.7 (4.00)	1.01 (0.97, 1.05)	***
Acute Kidney Injury				
No AKI	531 (58.5%)	157 (44.9%)	Reference	Reference
Stage 1	216 (23.8%)	88 (25.1%)	**1.43 (1.04, 1.97)**	1.02 (0.68, 1.53)
Stage 2	123 (13.5%)	80 (22.9%)	**2.67 (1.81, 3.94)**	1.50 (0.87, 2.57)
Stage 3	16 (1.8%)	17 (4.9%)	**4.67 (2.16, 10.12)**	1.54 (0.53, 4.46)
Lowest GCS				
<14	**43 (4.7%)**	**60 (17.1%)**	**5.18 (3.34, 8.01)**	**2.09 (1.20, 3.62)**
14	**158 (17.4%)**	**110 (31.4%)**	**2.71 (2.01, 3.67)**	**1.71 (1.19, 2.46)**
15	707 (77.9%)	180 (51.4%)	Reference	Reference
Assigned to fast treatment arm	470 (51.8%)	166 (47.4%)	0.85 (0.66, 1.10)	0.81 (0.60, 1.08)
Assigned to 0.9% NaCl treatment arm	470 (51.8%)	168 (48.0%)	0.86 (0.67, 1.11)	0.86 (0.64, 1.16)

Hypertension based on SBP

Reported values show mean (SD) or number of patients (percent of sample)

The odds-ratio for pH is the estimated multiplicative difference in odds for a 0.1 unit increase in pH; the odds-ratio for glucose is the estimated multiplicative difference for a 100 unit increase in glucose; all other odds ratios are the estimated multiplicative difference for a 1 unit increase (labs) or compared to the reference group.

Models adjusted for clinical site (not shown).

***
Sodium was not included in the multivariable model due to strong correlation with glucose-adjusted sodium. Dehydration was not included in the multivariable model due to 235 (19%) missing values.

Table 4:

Factors Associated with Elevated Mean Arterial Pressure at Presentation of DKA: Univariable and Multivariable Regression Models

	Not Hypertensive at Presentation (N = 1166)	Hypertensive at Presentation (N = 92)	Bivariable Odds-Ratio (95% CI)	Multivariable Odds-Ratio (95% CI)
Age Category				
0–4 years	**93 (8.0%)**	**16 (17.4%)**	**2.55 (1.24, 5.23)**	**3.71 (1.58, 8.74)**
5–9 years	256 (22.0%)	15 (16.3%)	0.85 (0.42, 1.73)	0.85 (0.37, 1.93)
10–14 years	552 (47.3%)	42 (45.7%)	1.11 (0.63, 1.97)	1.24 (0.66, 2.33)
15–18 years	265 (22.7%)	19 (20.7%)	Reference	Reference
Baseline pH	**7.17 (0.099)**	**7.08 (0.124)**	**0.48 (0.39, 0.58)**	**0.61 (0.44, 0.84)**
Baseline pCO2	26.3 (7.43)	23.1 (6.57)	**0.93 (0.90, 0.96)**	0.99 (0.94, 1.03)
Baseline BUN	17.4 (7.91)	15.6 (6.74)	0.97 (0.94, 1.00)	0.96 (0.91, 1.01)
Baseline Bicarbonate	**9.1 (3.22)**	**6.4 (2.21)**	**0.69 (0.62, 0.76)**	**0.84 (0.72, 0.98)**
Baseline Glucose	523.2 (156.04)	530.7 (189.13)	1.02 (0.89, 1.16)	0.96 (0.80, 1.16)
Baseline Glucose-Corrected Sodium	140.8 (5.14)	141.5 (6.20)	1.03 (0.98, 1.07)	1.00 (0.95, 1.05)
Dehydration severity based on weight change	5.3 (3.91)	6.0 (3.79)	1.03 (0.97, 1.09)	
Acute Kidney Injury at presentation				
No AKI	614 (52.7%)	42 (45.7%)	Reference	Reference
Stage 1	264 (22.6%)	24 (26.1%)	1.34 (0.78, 2.31)	1.30 (0.67, 2.51)
Stage 2	170 (14.6%)	16 (17.4%)	1.46 (0.74, 2.88)	1.30 (0.52, 3.26)
Stage 3	24 (2.1%)	4 (4.3%)	2.49 (0.77, 8.03)	2.47 (0.48, 12.78)
Unknown	94 (8.1%)	6 (6.5%)		
GCS at presentation				
<14	27 (2.3%)	5 (5.4%)	2.69 (0.99, 7.35)	1.11 (0.36, 3.46)
14	89 (7.6%)	13 (14.1%)	**2.17 (1.14, 4.11)**	1.21 (0.56, 2.65)
15	1050 (90.1%)	74 (80.4%)	Reference	Reference

Hypertension based on mean arterial pressure

Odds-ratio for pH is the estimated change in odds for a 0.1 unit increase in pH

Odds-ratio for Glucose is the estimated change in odds for a 100 unit increase in Glucose Other odds-ratios are for a 1 unit increase (labs) or compared to the reference group (age). Clinical site (not shown) is included in models.

Table 5:

Factors Associated with Elevated Mean Arterial Pressure at any Time During DKA: Univariable and Multivariable Regression Models

	Not Hypertensive During DKA (N = 1046)	Hypertensive at Some Time During DKA (N = 212)	Bivariable Odds-Ratio (95% CI)	Multivariable Odds-Ratio (95% CI)
Age Category				
0–4 years	**54 (5.2%)**	**55 (25.9%)**	**7.57 (4.46, 12.84)**	**14.72 (7.35, 29.50)**
5–9 years	232 (22.2%)	39 (18.4%)	1.19 (0.73, 1.94)	1.51 (0.83, 2.75)
10–14 years	514 (49.1%)	80 (37.7%)	1.09 (0.72, 1.67)	1.47 (0.88, 2.44)
15–18 years	246 (23.5%)	38 (17.9%)	Reference	Reference
Baseline pH	**7.17 (0.093)**	**7.09 (0.123)**	**0.47 (0.40, 0.55)**	**0.54 (0.41, 0.71)**
Baseline pCO2	26.6 (7.33)	23.2 (7.20)	**0.92 (0.90, 0.95)**	0.99 (0.95, 1.02)
Baseline BUN	17.2 (7.72)	17.3 (8.45)	1.00 (0.98, 1.02)	0.99 (0.96, 1.03)
Baseline Bicarbonate	**9.3 (3.17)**	**6.8 (2.74)**	**0.73 (0.68, 0.78)**	**0.89 (0.80, 0.99)**
Baseline Glucose	518.9 (155.23)	548.1 (172.72)	**1.10 (1.01, 1.20)**	0.98 (0.86, 1.12)
Baseline Glucose-Corrected Sodium	140.8 (4.91)	141.4 (6.55)	1.02 (0.99, 1.05)	1.00 (0.96, 1.04)
Dehydration severity based on weight change	5.2 (3.78)	6.2 (4.43)	**1.04 (1.00, 1.09)**	
Acute Kidney Injury				
No AKI	586 (56.0%)	102 (48.1%)	Reference	Reference
Stage 1	247 (23.6%)	57 (26.9%)	1.30 (0.89, 1.88)	0.98 (0.59, 1.61)
Stage 2	162 (15.5%)	41 (19.3%)	**1.67 (1.06, 2.65)**	0.89 (0.46, 1.73)
Stage 3	22 (2.1%)	11 (5.2%)	**3.58 (1.57, 8.13)**	1.50 (0.46, 4.93)
Unknown	29 (2.8%)	1 (0.5%)		
Lowest GCS				
<14	**57 (5.4%)**	**46 (21.7%)**	**6.68 (4.23, 10.56)**	**2.72 (1.47, 5.02)**
14	**195 (18.6%)**	**73 (34.4%)**	**3.30 (2.31, 4.70)**	**1.91 (1.23, 2.98)**
15	794 (75.9%)	93 (43.9%)	Reference	Reference
Assigned to the fast treatment arm			0.87 (0.64, 1.17)	0.81 (0.56, 1.17)
No	510 (48.8%)	112 (52.8%)		
Yes	536 (51.2%)	100 (47.2%)		
Assigned to the 0.90% treatment arm			0.83 (0.61, 1.12)	0.76 (0.53, 1.11)
No	507 (48.5%)	113 (53.3%)		
Yes	539 (51.5%)	99 (46.7%)		

Odds-ratio for pH is the estimated change in odds for a 0.1 unit increase in pH

Odds-ratio for Glucose is the estimated change in odds for a 100 unit increase in Glucose Other odds-ratios are for a 1 unit increase (labs) or compared to the reference group (age). Clinical site (not shown) included in models.

Table 6:

Factors Associated with Hypertension Severity Area Under the Curve (AUC): Univariable and Multivariable Zero-Inflated Negative Binomial Models.

	Univariable Ratio of AUC (95% CI)	Multivariable Ratio of AUC (95% CI)
Age Category		
0–4 years	1.14 (0.71, 1.83)	**1.81 (1.05, 3.10)**
5–9 years	0.75 (0.50, 1.15)	1.04 (0.65, 1.67)
10–14 years	1.26 (0.87, 1.82)	**1.54 (1.02, 2.34)**
15–18 years	Reference	Reference
Baseline pH	**0.74 (0.66, 0.83)**	**0.76 (0.62, 0.92)**
Baseline pCO$_2$ (mmHg)	**0.96 (0.95, 0.98)**	**0.96 (0.94, 0.99)**
Baseline BUN (mg/dL)	1.00 (0.98, 1.01)	0.99 (0.97, 1.01)
Baseline bicarbonate (mEq/L)	**0.91 (0.88, 0.94)**	1.04 (0.97, 1.12)
Baseline glucose (mg/dL)	1.01 (0.92, 1.10)	0.96 (0.87, 1.05)
Baseline sodium (mEq/L)	0.99 (0.96, 1.02)	***
Baseline glucose-corrected sodium (mEq/L)	0.99 (0.97, 1.02)	0.98 (0.95, 1.01)
Percentage dehydration	**0.96 (0.92, 1.00)**	***
Acute Kidney Injury		
No AKI	Reference	Reference
Stage 1	**1.45 (1.02, 2.05)**	1.32 (0.90, 1.94)
Stage 2	**1.70 (1.12, 2.57)**	**1.92 (1.15, 3.22)**
Stage 3	**2.58 (1.21, 5.51)**	2.51 (0.91, 6.97)
Lowest GCS		
<14	**1.84 (1.21, 2.80)**	1.38 (0.85, 2.25)
14	**1.67 (1.20, 2.32)**	1.37 (0.95, 1.98)
15	Reference	Reference
Assigned to fast treatment arm	1.12 (0.85, 1.48)	1.07 (0.79, 1.44)
Assigned to 0.9% NaCl treatment arm	1.04 (0.79, 1.36)	1.04 (0.78, 1.40)

Hypertension severity based on SBP

The ratio of AUC for pH is the estimated multiplicative difference for a 0.1 unit increase in pH; the ratio for glucose is the estimated multiplicative difference for a 100 unit increase in glucose; all other ratios are the estimated multiplicative difference for a 1 unit increase (labs) or compared to the reference group. Models adjusted for clinical site (not shown).

*** Sodium was not included in the multivariable model due to strong correlation with glucose-adjusted sodium. Dehydration was not included in the multivariable model due to 235 (19%) missing values.