Hypertension during Diabetic Ketoacidosis in Children

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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 Fluid Therapies Under Investigation in DKA 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. More severe acidosis and lower Glasgow Coma Scale 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 Glasgow Coma Scale scores during DKA treatment, suggesting that hypertension might be centrally mediated. *(J Pediatr 2020;223:156-63)*.

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 and several studies document abnormalities in cerebral blood flow during DKA.[4-12] It is possible that hypertension in children with DKA might reflect neurophysiologic 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 1 of 4 treatment arms to investigate the effects of fluid treatment variations on neurologic and neurocognitive outcomes. Data from frequent measurements of heart rate (HR) and blood pressure (BP) available for patients enrolled in

AKI	Acute kidney injury
AUC	Area under the curve
BP	Blood pressure
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
FLUID	Fluid Therapies Under Investigation in DKA
GCS	Glasgow Coma Scale
HR	Heart rate
MAP	Mean arterial pressure
PECARN	Pediatric Emergency Care Applied Research Network
SBP	Systolic blood pressure

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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 HR and BP 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 in PECARN from 2011 to 2016. Patients enrolled in the trial were randomized to 1 of 4 treatment arms that varied in regard to intravenous fluid infusion rate (more rapid vs slower rehydration) and fluid sodium content (0.9% NaCl vs 0.45% NaCl).[13,14] A total of 1389 patients were randomized between February 2011 and September 2016. The CONSORT flow chart for the primary outcome of the PECARN FLUID Study is provided (**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 before 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 elsewhere in this article.

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 BP (SBP), diastolic BP (DBP), or HR before DKA treatment initiation, or if there were fewer than 3 BP measurements within the first 6 hours of treatment.

Measures

Hemodynamic measurements were standardized for age and sex by calculating z-scores that indicate the number of SDs 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 (ie, >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 of greater than 2. Hypertension during DKA was defined as 2 or more SBP z-scores above 2 within any 2-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 of -2 within 2 hours. Hypotension during DKA treatment was defined as 2 or more SBP measurements with z scores of −2 or lower within any 2-hour interval during DKA treatment.

The area under the curve (AUC) and duration of hypertension were calculated using the trapezoidal method.[17] The 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, and the covariance between SBP and DBP estimated from the dataset.[15,16] 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 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 of age), rounded to the previous whole number. Sodium concentrations were corrected for glucose by adding 0.016 × (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, SDs, 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 nonhypertensive patients using means, SDs, 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. Owing to the substantial number of patients with AUCs of 0 (ie, no SBP >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 2-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 more than 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; SAS Institute, Cary, NC).

Results

During the enrollment period, 2848 children with DKA were eligible for the PECARN FLUID Study, and 1389 of these were randomized and enrolled.[13] Lack of enrollment was either owing to unwillingness to consent (n = 812) or lack of study personnel to enroll the patient (n = 631). There were 1258 patients (90.6%) with sufficient hemodynamic data during treatment for inclusion in the current analyses (Figure 1). Patients were excluded owing to lack of adequate documentation of vital signs before treatment (n = 93) or lack of sufficient SBP measurements (≥3) 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 the age- and sex-adjusted normal values. At their peak, HRs were almost 4 SD above the 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 the age-, height-, and sex-adjusted normal values. BP values increased during DKA treatment such that peak values were approximately 2 SD above the 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). HR and DBP were not correlated at presentation ($r = 0.03$), and peak values were only somewhat correlated ($r = 0.18$).

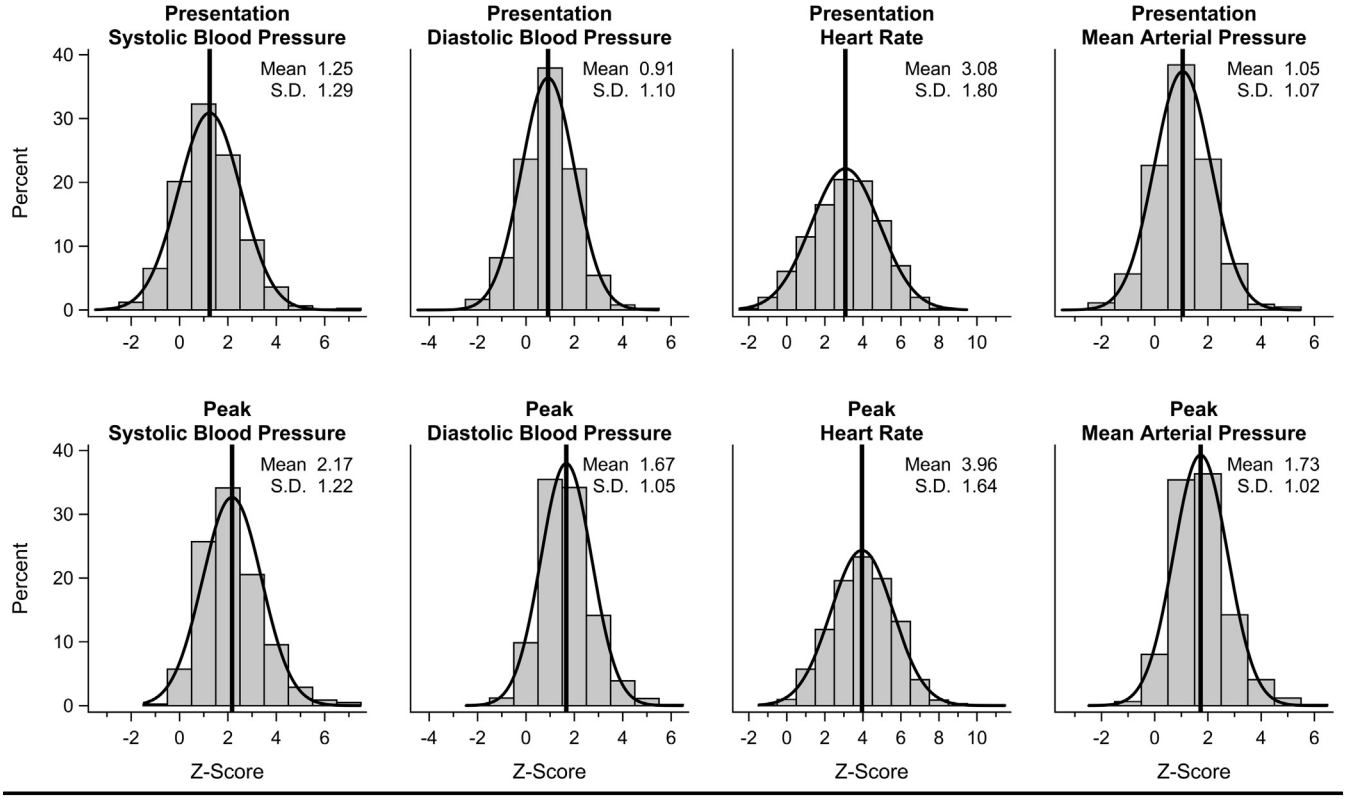

Figure 2. Distribution of blood pressure and heart rate z-scores.

Table I. Characteristics of patients with and without hypertension*

Characteristics	Hypertensive at presentation		Hypertensive at any time during DKA	
	No (n = 1104)	Yes (n = 154)	No (n = 908)	Yes (n = 350)
Mean age, y	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‡,§	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)

Values are mean ± SD or number (%).
*Hypertension based on SBP; characteristics compared using Wilcoxon rank-sum tests (age and dehydration) and χ^2 tests (all others).
†$P < .05$ comparing hypertension during DKA. Race: $P = .04$; clinically overt cerebral injury during hospitalization: $P = .003$. All other tests of differences between hypertension during DKA groups were not significant: $P \geq .05$.
‡$P < .05$ comparing hypertension at presentation. Percentage dehydration: $P = .04$; all other tests of differences between hypertension at presentation groups were not significant: $P \geq .05$.
§Missing dehydration data for 235 patients (19%): 158(17%) not hypertensive and 77 (22%) hypertensive.

Hypertension was documented at presentation in 154 of 1258 of DKA episodes (12.2%, Table I). Hypertension resolved rapidly (<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%), the BP 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 I). 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 (IQR, 1.2-5.0 hours). Among the 350 DKA episodes with hypertension, the median duration was 4.0 hours (IQR, 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 the 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 II. 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 III. 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 subanalyses, we used calculated MAP z-scores in place of SBP as the indicator of hypertension. Seven percent of children presented with MAP z-scores of 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 IV and Table V; available at www.jpeds.com).

Model results for hypertension severity (AUC for SBP z-scores) are provided in Table VI (available at www.jpeds.com). More severe acidosis (lower pH and lower pCO_2) and stage 2 AKI were associated with more severe

Table II. Factors associated with hypertension at presentation: univariable and multivariable logistic regression models

Factors	Not hypertensive at presentation (n = 1104)	Hypertensive at presentation (n = 154)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age category (y)				
0-4	99 (9.0)	10 (6.5)	0.62 (0.30-1.30)	0.90 (0.38-2.12)
5-9	239 (21.6)	32 (20.8)	0.82 (0.49-1.35)	1.03 (0.57-1.85)
10-14	524 (47.5)	70 (45.5)	0.83 (0.54-1.26)	0.93 (0.57-1.51)
15-18	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 (mm Hg)	**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	5.3 ± 3.88	6.0 ± 4.05	1.04 (0.99-1.09)	*
(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 OR for pH is the estimated multiplicative difference in the odds for a 0.1 unit increase in pH; the OR for glucose is the estimated multiplicative difference for a 100 unit increase in glucose; all other ORs are the estimated multiplicative difference for a 1 unit increase (laboratory tests) or compared with the reference group. Models adjusted for clinical site (not shown).
Values presented in bold indicate significant differences at $P < .05$.
*Sodium was not included in the multivariable model owing to strong correlation with glucose-adjusted sodium. Dehydration was not included in the multivariable model owing to 235 (19%) missing values.

Table III. Factors associated with hypertension occurring at any time during DKA treatment: Univariable and multivariable regression models

Factors	Not hypertensive during DKA (n = 908)	Hypertensive at some time during DKA (n = 350)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age category (y)				
0-4	69 (7.6)	40 (11.4)	1.41 (0.88-2.28)	1.64 (0.90-2.96)
5-9	201 (22.1)	70 (20.0)	0.84 (0.57-1.22)	0.97 (0.61-1.54)
10-14	443 (48.8)	151 (43.1)	0.81 (0.59-1.11)	0.97 (0.66-1.42)
15-18	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 (mm Hg)	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	5.2 ± 3.87	5.7 ± 4.00	1.01 (0.97-1.05)	*
AKI				
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 is based on SBP. Reported values show mean ± SD or number of patients (percent of sample). The OR for pH is the estimated multiplicative difference in odds for a 0.1 unit increase in pH; the OR 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 (laboratory tests) or compared with the reference group. Models adjusted for clinical site (not shown).
Values presented in bold indicate significant differences at $P < .05$.
*Sodium was not included in the multivariable model owing to strong correlation with glucose-adjusted sodium. Dehydration was not included in the multivariable model owing to 235 (19%) missing values.

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 finding 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 HRs, hypotension was rare. Furthermore, there were no associations between hypertension and the fluid infusion rate or the fluid sodium content. Therefore, the role of intravascular volume in the modulation of BP during pediatric DKA seems 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 1 child who was anephric. 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 antidiuretic hormone 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 depend 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 and reperfusion. Furthermore, hypocapnia has been proposed as a factor responsible for cerebral hypoperfusion before 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 before 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, despite 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 and lactate concentrations and increases in BP. Higher levels of ambient adenosine triphosphate 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 physiologic connection between intracranial pathology and hypertension would explain the 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 or as a result of elevated angiotensin II levels.[25-28] 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 (Myers S. Acute kidney injury in children with diabetic ketoacidosis. Personal Communication, 2019).

Our data highlight several important issues about the monitoring of children with DKA. First, BP regulation during DKA seems to be influenced by factors other than intravascular volume, and BP measurements therefore should not be relied on in decision making about fluid administration. Instead, other factors such as HR, clinical assessments of peripheral perfusion, trends in laboratory indicators of circulatory volume (blood urea nitrogen 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 BP measurements were not standardized across centers or between different care sites (emergency department, critical care unit, or ward) at each study center. This difference may have caused some variability or errors in measurements. We suspect, however, that errors in measurements were infrequent, because all participating centers were tertiary care children's hospitals with rigorous nursing standards. Furthermore, statistical analyses were stratified by center. Owing to the low frequency of clinically overt cerebral injury during DKA, decreases in GCS scores were the primary neurologic outcomes. Whether more modest decreases 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 subclinical cerebral edema measured by magnetic resonance imaging. In addition, patients with GCS scores of less than 12 were excluded after the first 2 years of the parent study, decreasing 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. Because 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, despite 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. ■

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50 Years Ago in *The Journal of Pediatrics*

Amblyopia Screening: An Update

Giles CL. Detection of amblyopia in the preschool child. J Pediatr 1970;77:309-10.

Nowadays, amblyopia is a treatable condition yet still is one of the leading causes of monocular visual disability, affecting 2%-5% of children.[1] Thanks to high-quality evidence from randomized trials, we know that adequate early treatment (patching and/or atropine penalization) results in better visual outcomes and improves the prognosis. Visual screening plays a critical role in the identification and treatment of preschool children with visual impairment.

Fifty years ago, Dr Giles recognized the need for better screening methods for early detection of amblyopia. At that time, the use of the "Illiterate E" modified Snellen chart was routine. However, this chart posed difficulties, such as the time and effort needed to teach children how to use it. Dr Giles proposed a magnified version to the Allen test, putting the optotypes in the waiting room so that the patient could be familiarized with the figures before the examination.

We now know that the Allen chart is not the best method to screen and follow visual acuity because it is not uniform in optotype size and does not follow a logarithmic scale. The American Academy of Ophthalmology, American Association of Pediatric Ophthalmology and Strabismus, and The US Preventive Services Task Force recommend screening using new visual acuity tests such as LEA and HOTV charts, which use figures and letters for easier and more accurate testing in preliterate children. The importance of these tests is their reproducibility and reliability.[1]

New technologies to screen children and those with different abilities have emerged. Cameras (Plusoptix, I-Screen), refractometers (Retinomax), and even smartphone applications have been efficacious in detecting amblyopia and risk factors such as ametropias and strabismus. These technologies have changed the landscape of screening. Although they offer new solutions for preschool children who struggle with the standard HOTV or LEA charts, these tests will continue to evolve.

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Appendix

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Additional co-investigators of the PECARN DKA FLUID Study Group at the time of the design and initiation of the study are acknowledged in the table below.

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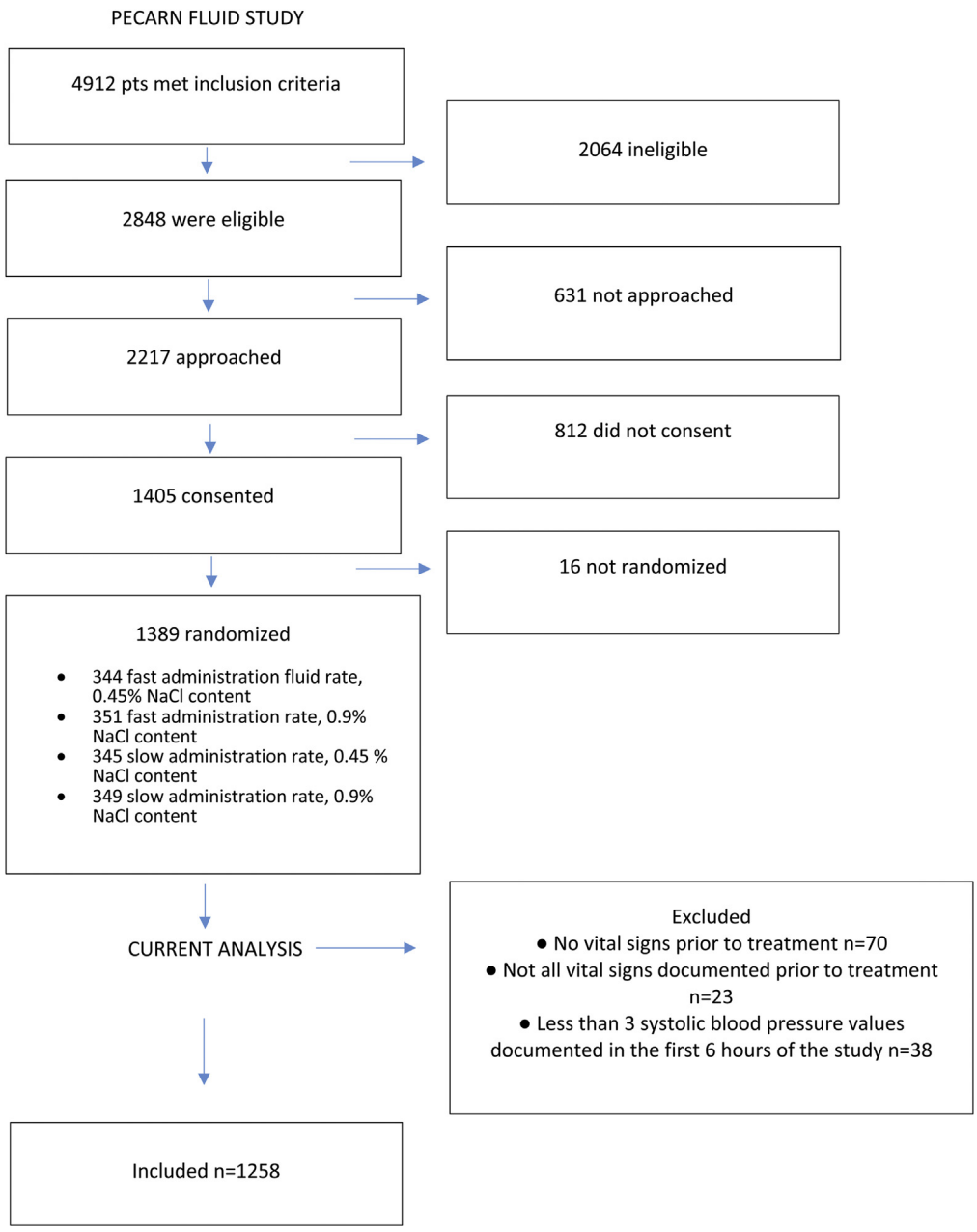

Figure 1. Patient Inclusion in the PECARN FLUID Study and Current Analysis.

Table IV. Factors associated with elevated MAP at presentation of DKA: Univariable and multivariable regression models

Variables	Not hypertensive at presentation (n = 1166)	Hypertensive at presentation (n = 92)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age category (y)				
0-4	**93 (8.0)**	**16 (17.4)**	**2.55 (1.24-5.23)**	**3.71 (1.58-8.74)**
5-9	256 (22.0)	15 (16.3)	0.85 (0.42-1.73)	0.85 (0.37-1.93)
10-14	552 (47.3)	42 (45.7)	1.11 (0.63-1.97)	1.24 (0.66-2.33)
15-18	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 pCO_2	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)	–
AKI 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

Values are mean ± SD or number (%) unless otherwise indicated. Hypertension based on MAP. OR for pH is the estimated change in odds for a 0.1 unit increase in pH. OR for glucose is the estimated change in odds for a 100 unit increase in glucose. Other ORs are for a 1 unit increase (laboratory tests) or compared with the reference group (age). Clinical site (not shown) is included in models. Values presented in bold indicate significant differences at $P < .05$.

Table V. Factors associated with elevated MAP at any time during DKA: Univariable and multivariable regression models

Variables	Not hypertensive during DKA (n = 1046)	Hypertensive at some time during DKA (n = 212)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age category (y)				
0-4	**54 (5.2)**	**55 (25.9)**	**7.57 (4.46-12.84)**	**14.72 (7.35-29.50)**
5-9	232 (22.2)	39 (18.4)	1.19 (0.73-1.94)	1.51 (0.83-2.75)
10-14	514 (49.1)	80 (37.7)	1.09 (0.72-1.67)	1.47 (0.88-2.44)
15-18	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 pCO_2	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)**	–
AKI				
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)	–	–

OR for pH is the estimated change in odds for a 0.1 unit increase in pH. OR for Glucose is the estimated change in odds for a 100 unit increase in Glucose. Other ORs are for a 1 unit increase (laboratory tests) or compared with the reference group (age). Clinical site (not shown) included in models.
Values presented in bold indicate significant differences at $P < .05$.

Table VI. Factors associated with hypertension severity AUC: Univariable and multivariable zero-inflated negative binomial models

Variables	Univariable ratio of AUC (95% CI)	Multivariable ratio of AUC (95% CI)
Age category (y)		
0-4	1.14 (0.71-1.83)	**1.81 (1.05-3.10)**
5-9	0.75 (0.50-1.15)	1.04 (0.65-1.67)
10-14	1.26 (0.87-1.82)	**1.54 (1.02-2.34)**
15-18	Reference	Reference
Baseline pH	**0.74 (0.66-0.83)**	**0.76 (0.62-0.92)**
Baseline pCO_2 (mm Hg)	**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)**	*
AKI		
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 is based on SBP. The ratio of the 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 (laboratory tests) or compared with the reference group. Models adjusted for clinical site (not shown).

Values presented in bold indicate significant differences at $P < .05$.

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