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Clinical and Laboratory Predictors of Dehydration Severity in Children with Diabetic Ketoacidosis

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Dr. Trainor conceptualized and designed the study, supervised, acquired, analyzed, and interpreted the data, and drafted and critically revised the manuscript for important intellectual content. Dr. Glaser obtained funding, conceptualized and designed the study, supervised, acquired, analyzed, and interpreted the data, drafted and critically revised the manuscript for important intellectual content. Dr. Kuppermann obtained funding, conceptualized and designed the study, supervised, acquired, analyzed, and interpreted the data, drafted and critically revised the manuscript for important intellectual content, and provided administrative, technical, and material support. Mr. Olsen and Dr. Casper conceptualized and designed the study, had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis, drafted portions of the manuscript, and critically revised the manuscript for important intellectual content. Drs. Tzimenatos, Stoner, Brown, McManemy, Schunk, Quayle, Nigrovic, Rewers, Myers, Bennett, Kwok, and Ghetti conceptualized and designed the study, supervised, acquired, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Objectives: Our primary objective was to characterize the degree of dehydration in children with diabetic ketoacidosis (DKA) and identify physical examination and biochemical factors associated with dehydration severity. Secondary objectives included describing relationships between dehydration severity and other clinical outcomes.

Methods: In this cohort study, we analyzed data from 753 children with 811 episodes of DKA in the Pediatric Emergency Care Applied Research Network (PECARN) FLUID Study, a randomized clinical trial of fluid resuscitation protocols for children with DKA. We used multivariable regression analyses to identify physical examination and biochemical factors associated with

dehydration severity, and we described associations between dehydration severity and DKA outcomes.

Results: Mean dehydration was 5.7% (SD 3.6%). Mild (0-<5%), moderate (5-<10%), and severe (≥10%) dehydration were observed in 47% (N=379), 42% (N=343), and 11% (N=89) of episodes, respectively. In multivariable analyses, more severe dehydration was associated with new onset of diabetes, higher blood urea nitrogen (BUN), lower pH, higher anion gap, and diastolic hypertension. However, there was substantial overlap in these variables between dehydration groups. Mean length of hospital stay was longer for patients with moderate and severe dehydration, both in new onset and established diabetes.

Conclusions: Most children with DKA have mild-to-moderate dehydration. Although biochemical measures were more closely associated with the severity of dehydration than clinical assessments, neither were sufficiently predictive to inform rehydration practice.

Introduction

Accurate assessment of dehydration has long been considered necessary for planning rehydration in children with diabetic ketoacidosis (DKA). However, previous studies have found that estimating dehydration severity using physical examination criteria is challenging,[2, 3] and is particularly difficult in children with DKA.[4, 5] Poor agreement between estimated and measured degrees of dehydration has been demonstrated.[4, 6] Therefore, controversy exists on how to best estimate degree of dehydration at the start of therapy. Some guidelines recommend empirical assumption of a standard level of dehydration (6–8%) for all children with DKA to plan fluid replacement.[4, 6] Others argue against assuming a uniform fluid deficit and insist that estimates of dehydration need to be individualized.[7] All existing studies have involved only single centers and limited sample sizes.[4–6, 8] The PECARN FLUID Study found that a wide range of intravenous fluid infusion rates were safe for children with DKA and concluded that fluid infusion rates should be tailored to individual needs.[9] Although fluid infusion is not associated with cerebral injury, the frequency and severity of other adverse outcomes, such as acute kidney injury,[10–12] intestinal necrosis,[13] and thromboses,[14] are likely affected by rates of fluid infusion. Appropriately hydrating children may be helpful for reducing risk of these rare but serious adverse events. Therefore, determining which factors provide the most reliable information on dehydration severity is important. Our main objective was to characterize the degree of dehydration at presentation in a large cohort of children with DKA and to identify physical examination and biochemical factors associated with severity of dehydration, using data from a large, multicenter study of children with DKA. Secondary objectives included describing relationships between dehydration severity and other clinical outcomes such as mental status decline during treatment, time to initiation of subcutaneous insulin, and hospital length of stay.

Methods

Study Design and Setting

For this analysis, patient data were obtained through the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Study

(ClinicalTrial.gov NCT00629707), a randomized clinical trial of fluid resuscitation protocols for children with DKA.[9] In the parent study, we enrolled patients from 13 emergency departments (EDs) in PECARN which included 1255 patients younger than 18 years with 1389 distinct episodes of DKA (blood glucose level of >300 mg/dL [16.7 mmol/L] and either a venous pH of <7.25 or a serum bicarbonate level of <15 mmol/L) from 2011 to 2016. The PECARN FLUID Trial compared four fluid rehydration protocols to treat children with DKA.[9] The four arms of the trial included variations of rehydration strategies frequently used in the U.S. Exclusion criteria are described elsewhere and included conditions unrelated to DKA that affect mental status or cognitive abilities, and/or substantial treatment for DKA prior to transfer to the study centers.[1] During the parent study, we noted that weights measured on different scales within each site were not sufficiently accurate for use in calculating percentage dehydration. We therefore switched to portable digital standardized study scales for all enrolled patients starting in the second year of the study, such that pre- and post-treatment weights were obtained on the exact same scale and measured with patients in a gown without shoes.

Selection of Participants

Of the 1389 DKA episodes enrolled in the main PECARN FLUID trial, 811 were included in this analysis. We excluded 578 episodes due to missing data on discharge weight, enrollment prior to use of standard study scales, discharge more than 96 hours after enrollment such that discharge weight may no longer accurately reflected percent dehydration, or errors in recorded weights (Figure 1). Excluded patients (Table 1a: online only) had slightly greater hypocapnia, slightly higher baseline glucose and BUN levels, and creatinine z-scores. Excluded patients more frequently had Glasgow Coma Scale (GCS) scores of 14 or lower than included patients.

Measurements

Percent dehydration was calculated on the basis of change in body weight from admission to discharge, according to the following formula, $(discharge\ weight - admission\ weight) \div discharge\ weight \times 100\%$. Dehydration severity was categorized a priori as mild (0 to <5%), moderate (5 to <10%), or severe (10% or more). Initial weights were taken after informed consent and randomization. Most patients (82%) were weighed before receiving any treatment for DKA. A maximum of 10 ml/kg fluid bolus was infused prior to weight being obtained in the other 18%.

Enrolling and/or treating physicians recorded initial physical examination findings in real time. Study personnel recorded laboratory findings and mental status during treatment, hospital length of stay and total volume of intravenous fluids infused during hospitalization. Standard laboratory data including venous pH, serum glucose, and electrolytes were recorded as the first values measured prior to randomization. Arterial pH measurements were converted to venous by subtracting 0.035.[15] Creatinine values were age-adjusted using age-based reference values to calculate z-scores, where a z-score of 1 represents one standard deviation above the mean for age.[16] Anion gap was calculated from serum sodium, potassium, chloride and bicarbonate values. Heart rate at presentation was recorded as the first heart rate measured prior to randomization, adjusted for age using the Centers for

Disease Control and Prevention (CDC) reference to determine heart rate z-scores.[17] Systolic and diastolic blood pressures were adjusted for age, sex, and height using the National Heart, Lung, and Blood Institute (NHLBI) reference[18] and CDC growth charts to calculate normalized heights.[19] When height was unknown (2.8% of those with blood pressures), 50th percentile height for age and sex was assumed. Capillary refill time at presentation was recorded by study personnel as <2 seconds, 2–5 seconds, or >5 seconds. Weight z-scores adjusted for sex and age were calculated using World Health Organization growth charts for children under 24 months of age and Centers for Disease Control growth charts for children 24 months and older.[20, 21]

Outcomes

Our primary outcome measure was degree of dehydration at presentation to the ED. We assessed physical examination and biochemical factors associated with dehydration severity. We also described relationships between dehydration severity and other clinical outcomes such as administering additional IV fluids outside of treatment protocol, hospital length of stay, time to transition to subcutaneous insulin treatment, and mental status decline during treatment.

Statistical Analysis

We described patient demographic and clinical characteristics using counts and relative frequencies, means and standard deviations, and medians and interquartile ranges. We estimated differences in means and differences in proportions with 95% confidence intervals. To assess the extent to which estimates of dehydration severity might have been affected by receipt of IV fluids prior to the baseline weight measurements, percent dehydration was compared between children whose weights were measured after initiation of IV fluids (18%) to those for whom weights were measured prior using a difference in means and 95% confidence interval.

Regression Models: Dehydration severity and clinical and laboratory measures

A series of multiple multinomial logistic regression models were used to examine associations between dehydration severity and clinical and laboratory measures. Dehydration was treated as a 3-level categorical outcome, with mild dehydration as the reference level. We estimated odds-ratios and 95% confidence intervals, comparing moderate vs. mild and severe vs. mild dehydration using a generalized logit link function. All statistical models included age, sex, and new onset of diabetes to address possible physiological differences between patients in kidney function or physical findings related to these variables. Partially-adjusted models were fit with those covariates plus each of the following variables one at a time: heart rate, systolic blood pressure, diastolic blood pressure, capillary refill time (≥2 vs <2 seconds), BUN, creatinine, glucose-corrected sodium, bicarbonate, pH, pCO_2, glucose, and anion gap. We then fit a final adjusted model including all covariates except bicarbonate, which was excluded due to known correlation with pH. We repeated the multivariable analyses in the subset of patients who had baseline weights measured before IV therapy was initiated. We assessed fit of the final models using a Hosmer-Lemeshow goodness-of-fit statistic. Area under the receiver operating characteristic curve (AUC) was estimated after dichotomizing the outcome into severe vs.

mild or moderate dehydration. Collinearity was examined using variance inflation factors. We plotted the estimated probability of mild, moderate, and severe dehydration for each DKA visit based on the final model versus significantly associated biochemical variables in order to illustrate associations. Expected probabilities and 95% confidence intervals, calculated separately for new onset DKA and known diabetes and assuming mean values of all other variables, were plotted to describe the associations.

Dehydration severity and clinical outcomes

We also sought to explore how fluid protocol adherence and other clinical outcomes were related to severity of dehydration. In the parent FLUID trial, patients were randomly assigned to receive either a 10 ml/kg 0.9% NS fluid bolus over ≤ 60 minutes, followed by a slower fluid resuscitation rate (designed to replete a 5% estimated fluid deficit plus maintenance evenly over 48 hours), or a 20 ml/kg 0.9% NS fluid bolus over ≤ 60 minutes followed by a faster fluid resuscitation rate (designed to replete a 10% estimated fluid deficit, half over the first 12 hours, half over the subsequent 24 hours). Non-bolus fluids were randomized to either 0.9% NS or 0.45% NS. Clinicians were encouraged to follow the assigned treatment protocol, however, adjustments to fluid infusion rates were allowed if these were felt to be necessary for clinical care. Administration of fluids in excess of those prescribed by the protocol suggests that clinicians' estimates of dehydration based on clinical judgement exceeded those assumed in the assigned study arm. Therefore, determining how these deviations from study protocol correlate with actual percent dehydration provides insights into accuracy of clinical judgement for estimating dehydration.

We described the following clinical measures in each of the dehydration severity groups using counts and relative frequencies or means and standard deviations: time to transition to subcutaneous insulin; hospital length of stay described separately for new onset and previously diagnosed patients; mental status decline measured by a confirmed drop in GCS <14. We similarly described measures related to the study protocol: patient received more than the IV bolus amount prescribed per FLUID protocol; patient received more than the fluid amount prescribed per FLUID protocol; volume of additional fluid received when the patient received more than prescribed by the FLUID protocol (ml/kg). We calculated differences in means and proportions for the moderate vs mild groups and the severe vs mild groups along with 95% confidence intervals for each comparison. Analyses were performed using SAS/STAT software (version 9.4, SAS Institute Inc., Cary NC, USA).

Results

Characteristics of study participants are described in Table 1. Of the 811 total DKA episodes analyzed, 47% (N=379) were classified as having mild dehydration, 42% (N=343) as moderate, and 11% (N=89) as severe. The mean percent dehydration in the cohort overall was 5.7% with a standard deviation of 3.6%. The median percent dehydration was 5.3% with an interquartile range (IQR) of 3.1% to 7.8%. Within each classification group, median (IQR) percent dehydration was 3.0 (1.9, 4.0) for the mild dehydration group, 6.8 (5.9, 8.2) for the moderate group, and 11.3 (10.6, 13.3) for the severe group. Eighty-two

percent of patients had initial weights measured prior to receipt of any fluid. Those with weights measured prior to receipt of fluid were similar, though somewhat less dehydrated (mean 5.6%) compared to those with weights measured after fluid initiation (mean 6.2%, Difference in means: 0.6%, 95% CI: −0.1, 1.2%).

In univariable analyses, dehydration severity groups differed significantly in age, sex, new onset of diabetes (vs. known diabetes), GCS score, and all biochemical variables except BUN and partial pressure of CO_2. Among clinical characteristics, age-adjusted mean heart rates did not differ across dehydration severity groups. Systolic and diastolic blood pressure z-scores were significantly higher in the severe dehydration group compared to the mild group. Capillary refill time varied, with substantial overlap between groups. Of the 379 patients in the mild dehydration group, 224 (59%) had < 2 second capillary refill time compared to 38 (43%) in the severe dehydration group. Notably, more than one-third of patients in the mild dehydration group had prolonged capillary refill time (Table 1).

In partially adjusted models (adjusted for age, sex, and new onset versus known type 1 diabetes) all biochemical variables except partial pressure of CO_2 were significantly associated with dehydration severity. In the final adjusted model, new onset of diabetes maintained a significant association with dehydration severity. A significant association with mild vs. moderate dehydration persisted for pH and anion gap, and BUN maintained a consistent significant association with severe vs mild dehydration severity. However, there was substantial overlap in these variables between dehydration groups.

Figure 2 shows the relationships between the probability of mild, moderate, or severe dehydration and values of pH, BUN, and anion gap. The probability of moderate dehydration decreased with increased pH and decreased anion gap. The probability of severe dehydration was mainly reflected in the BUN concentration, with increased probability of severe dehydration in children with new-onset of diabetes and BUN concentrations above 25 mg/dL or above 30 mg/dL for children with previously diagnosed diabetes. However, substantial overlap of the 95% CIs for expected probabilities limited the predictive value of the variables.

Higher diastolic blood pressure was associated with dehydration severity in the comparison of severe versus mild dehydration but not moderate versus mild dehydration. Higher systolic blood pressure was associated with dehydration severity in the comparison of moderate versus mild dehydration. (Table 2). Using the variables included in the final adjusted model to calculate receiver operating characteristic curves resulted in an area under the curve to predict severe dehydration of 0.76 (Figure 1a). Results from models fit to the 667 visits whose initial weight was measured prior to IV therapy were similar to those from the full cohort (Table 2a) with an area under the curve of 0.79 to predict severe dehydration.

For patients with either new onset of diabetes or known diabetes, mean length of hospital stay was longer for both severely and moderately dehydrated patients vs mildly dehydrated patients. Time to transition to subcutaneous insulin was also longer in patients with more severe dehydration. There were no significant differences in frequency of mental status decline between dehydration severity groups. (Table 3) Three patients in this study cohort

had clinically apparent cerebral injury (two with mild and one with moderate dehydration) and none died. We also examined whether patients received more fluid based on their dehydration severity. Dehydration severity was not associated with either the amount of additional fluid given or receiving more initial bolus fluids than the prescribed amount. (Table 3)

Limitations

Several potential limitations of our study relate to enrollment. Although we did not enroll children known to have type 2 diabetes at the time of hospitalization, children initially presumed to have type 1 diabetes are sometimes found months or years later to have type 2 diabetes. We did not reassess medical records of enrolled patients to verify that the diagnosis of type 1 diabetes was not later changed to type 2 diabetes. However, there is no physiologic basis to suspect that predictors of dehydration severity during DKA would differ substantially in children with type 1 versus type 2 diabetes.

Some more severely dehydrated patients may have been excluded from the parent study because treatment with substantial volumes of fluid before transfer to a PECARN ED would have made these patients ineligible for enrollment in the parent FLUID study. In addition, the mean percent dehydration in the full cohort may have been slightly underestimated because a small number of patients received up to 10 ml/kg of intravenous fluid prior to measurement of baseline weight. However, mean weights were minimally different between patients who were weighed before or after the initial intravenous fluid bolus. Furthermore, a separate analysis of only patients with baseline weights measured before intravenous fluid therapy did not differ substantially from the main analysis.

Patients were discharged when they were tolerating oral intake and had transitioned to subcutaneous insulin regimens, however, discharge may have occurred prior to full rehydration in some patients. This may have caused a slight underestimation of the degree of dehydration for these patients. Overall, the percentage dehydration documented in this cohort is likely to slightly underestimate that of the pediatric DKA population as a whole.

Discussion

To our knowledge, this is the first large prospective, multi-center evaluation of clinical and biochemical factors associated with dehydration severity in children with DKA. The median percent dehydration observed in our study population, 5.3%, was similar to that observed in three previous smaller studies with median dehydration percentages in their cohorts of 5.2% (N=66)[6], 5.7% (N=42)[5] and 6.2% (N=33)[8] respectively. An older study reported an overall median dehydration rate of 8.7% (N=37).[4] Prior to these studies, dehydration was more commonly estimated to be approximately 10% for children in DKA.[22–24] These studies had similar limitations to our own, relying on discharge weights to estimate percent loss of body weight as a proxy for dehydration. A single study[8] reported no significant difference between discharge weight and follow-up weight at the first clinic visit after discharge, suggesting that discharge weight is an appropriate proxy.

Our data suggest that distinguishing dehydration severity based on physical examination parameters is generally inaccurate. Clinical assessments such as vital signs and capillary refill time were not reliably associated with dehydration severity. Similarly, clinicians' decisions to administer additional intravenous fluids above those prescribed by the treatment protocol were not strongly correlated with dehydration severity, suggesting that clinicians' assessments of the need for additional fluids reflect additional factors beyond dehydration severity.

Although capillary refill time was significantly different between dehydration severity groups, there was substantial overlap between groups, limiting its clinical utility. In addition, capillary refill time did not retain a significant association with dehydration severity in the multivariable model, suggesting that this measure was no longer useful for predicting dehydration severity after accounting for other covariates, particularly laboratory measures. Body site and skin and ambient temperatures are all known to influence capillary refill time measurement[25] and this may have contributed to the lack of utility of this finding in our study.

Associations between heart rate and blood pressure z-scores and dehydration severity also were inconsistent and some associations were unexpected. In the multivariable model, higher diastolic blood pressure was associated with severe dehydration. Although this finding appears counterintuitive, several reports have documented that paradoxical hypertension often occurs in children with DKA and is more frequent among those with more severe acidosis.[26] Our findings similarly reflect the complex regulation of hemodynamic state during DKA in children.

The lack of consistent associations between hemodynamic and clinical measures and dehydration severity in children with DKA may in part be related to variations in intravascular volume loss among these children. Weight-based measures of dehydration reflect total body fluid losses. However, during DKA, intravascular volume is often relatively preserved as a result of high glucose and/or sodium concentrations that create osmotic gradients to retain fluid volume within the vasculature. The extent to which this process occurs in any given child will depend on the relative losses of sodium and free water, and the degree of hyperglycemia, which may vary independent of dehydration severity. In comparison to clinical parameters, laboratory measures were more strongly linked to dehydration severity, particularly BUN and pH. However, substantial overlap in 95% confidence intervals for the predictive variables did not allow for development of a clinically useful prediction rule to inform rehydration practice.

Contrary to prevalent beliefs that slower rehydration prevents cerebral injury in DKA, the PECARN FLUID trial did not find any significant differences in outcomes associated with patients randomized to 20 ml/kg fluid bolus and more rapid rehydration for a presumed 10% fluid deficit versus 10 ml/kg fluid bolus and slower rehydration for a presumed 5% fluid deficit.[8] Notably, there was a trend towards improved acute neurological status among the most severely ill (highly acidotic, more elevated BUN) in the faster fluid arms. Given the demonstrated risk of acute kidney injury,[10–12] and the risks of other complications potentially related to organ hypoperfusion,[13, 27, 28] we recommend a more uniform approach

to rehydration for children with DKA to begin with a 20 ml/kg bolus of isotonic fluid, a standard for dehydrated pediatric patients not in DKA. Based on our data, we further recommend an assumption of ~6% dehydration (average for the whole cohort) to calculate total replacement fluids in patients with established diabetes presenting in DKA and an assumption of ~8% dehydration (average dehydration in the moderate and severe groups) for patients with new onset of diabetes or patients with severe acidosis (pH<7.1; lower quartile of pH) or elevated BUN (BUN>20 mg/dL; upper quartile of BUN).

This study of dehydration severity in a large, multi-center, prospectively collected cohort of children with DKA demonstrates that most have mild-to-moderate dehydration, and that children with new onset of diabetes, elevated BUN, and more severe acidosis tend to be more severely dehydrated. Although our data show that biochemical measures better distinguish severity of dehydration than clinical assessments, neither was sufficient to develop a customized approach to calculating fluid deficits based on these characteristics.

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Abbreviations:

DKA	Diabetic ketoacidosis
BUN	blood urea nitrogen
FLUID	Fluid Therapies Under Investigation
DM	diabetes mellitus
CDC	Centers for Disease Control and Prevention
ED	Emergency Department

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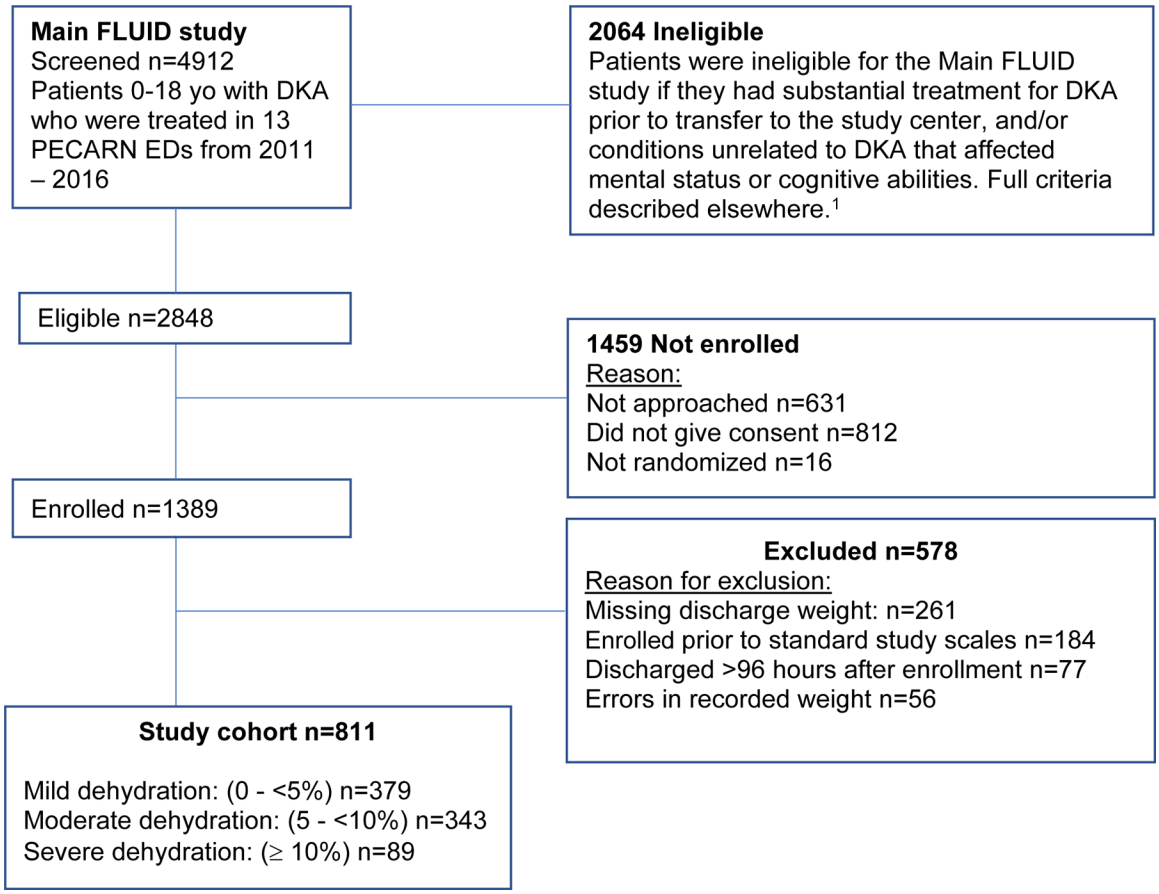

Figure 1:
Study participants after exclusions

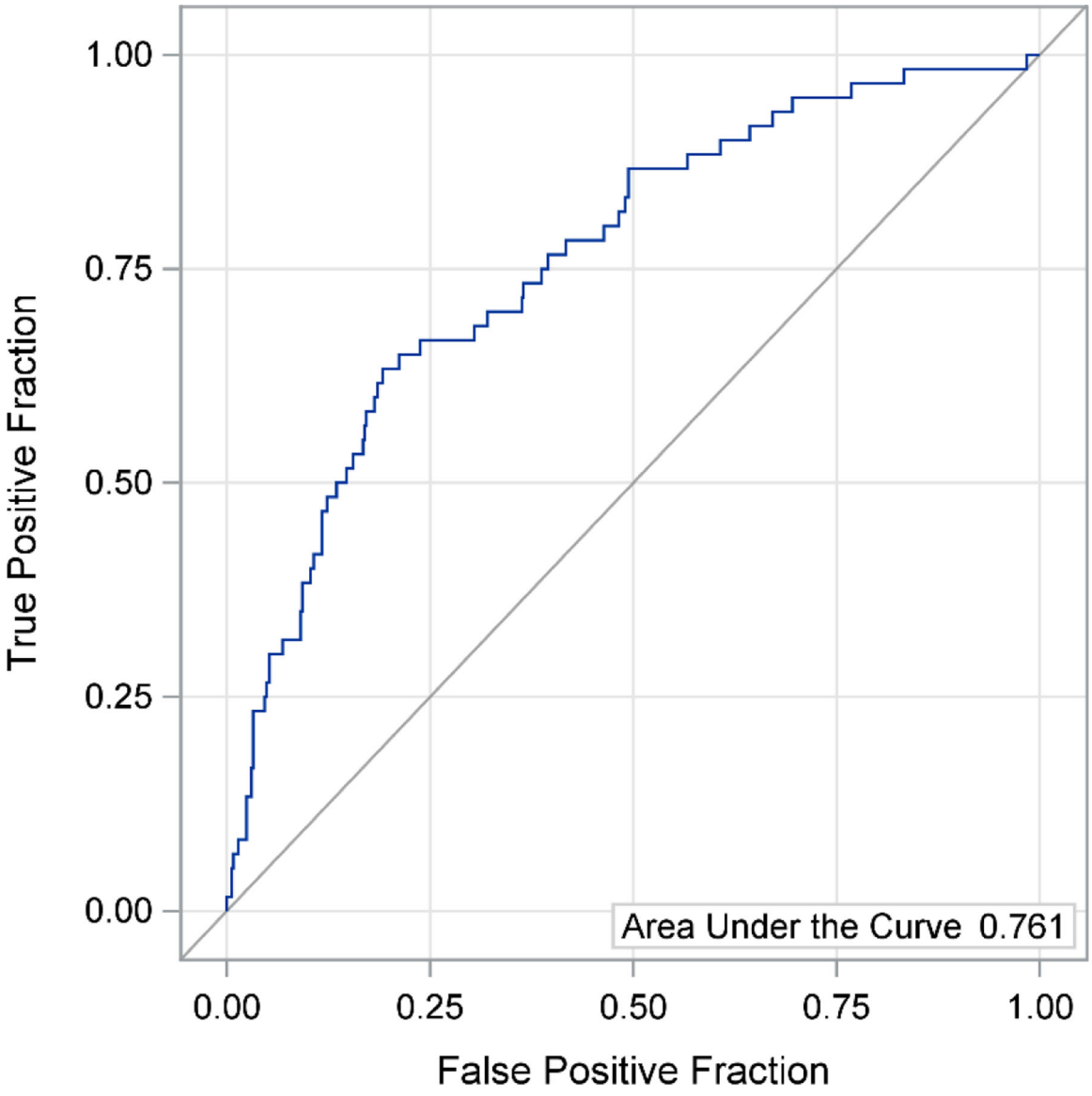

Figure 1a.

(Online only) Area under the receiver operating characteristic curve (AUC) of severe vs. mild or moderate dehydration and predictors: heart rate, systolic blood pressure, diastolic blood pressure, capillary refill time (≥2 vs <2 seconds), BUN, creatinine, glucose-corrected sodium, pH, pCO2, glucose, and anion gap.

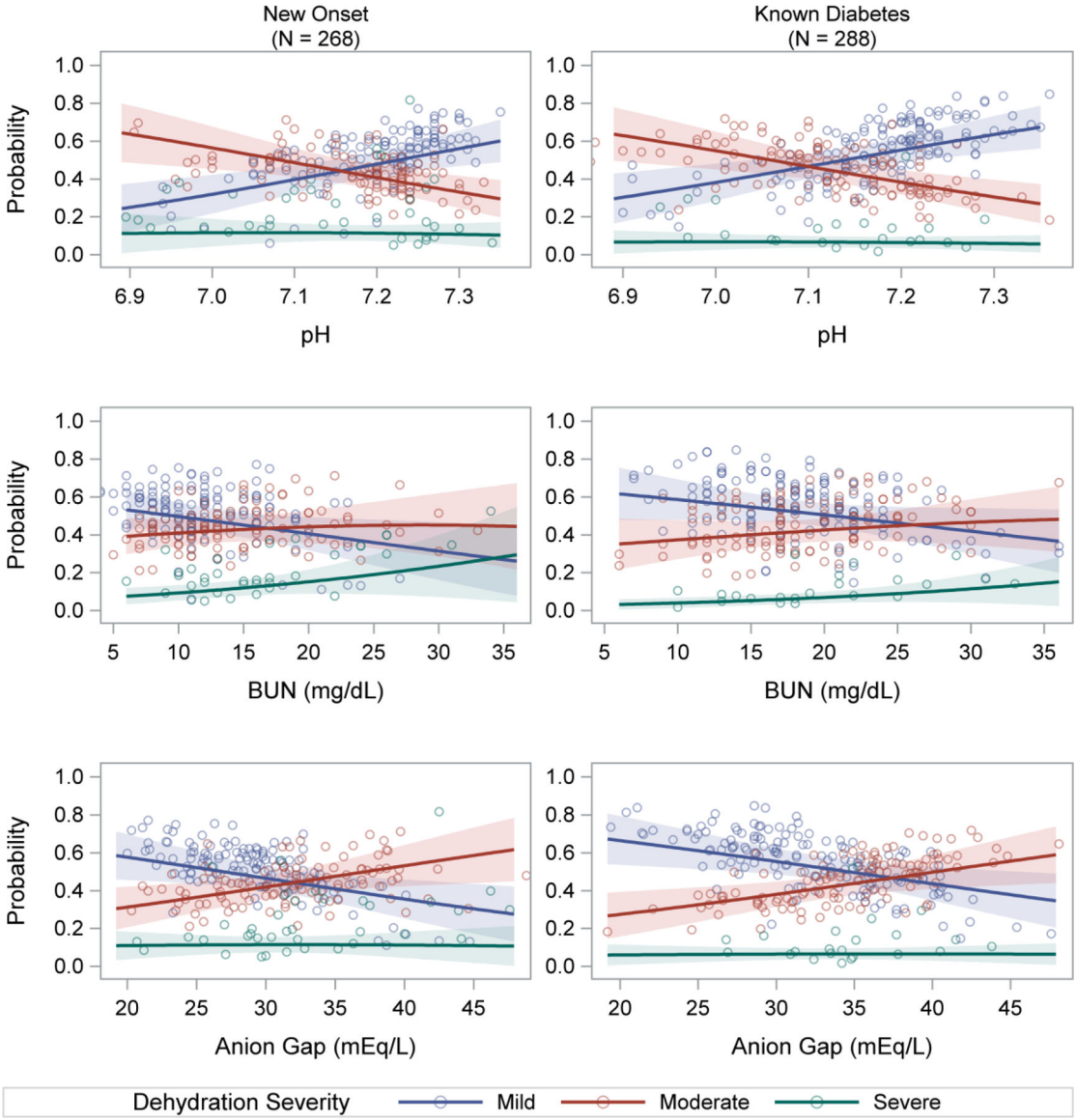

Figure 2:

Associations between estimated probabilities of mild, moderate, and severe dehydration and biochemical variables in children with new-onset and previously diagnosed diabetes.

Estimated probabilities are ploted as circles

Lines presented the expected probablity assuming mean values of all other covariates

Pointwise 95% confidence limits are shown as shaded regions

Table 1.

Clinical and biochemical characteristics of dehydration severity groups. Mean (SD) or N (%).*†

	Mild (0-<5%) (N = 379)	Moderate (5-<10%) (N = 343)	Severe (10% or more) (N = 89)	Difference Between Moderate & Mild (95% CI)	Difference Between Severe & Mild (95% CI)
Age (years)	11.8 (3.8)	11.9 (3.8)	10.6 (4.1)	0.1 (−0.5, 0.7)	−1.2 (−2.2, −0.3)
Sex: Male	157 (41.4%)	160 (46.6%)	49 (55.1%)	5.2% (−2.0, 12.5)	13.6% (2.2, 25.1)
New onset	163 (43.0%)	171 (49.9%)	57 (64.0%)	6.8% (−0.4, 14.1)	21.0% (9.9, 32.2)
Baseline BUN (mg/dL)	16.1 (6.4)	16.9 (6.3)	18.5 (10.5)	0.9 (−0.1, 1.8)	2.4 (−0.0, 4.9)
Baseline Creatinine z-score	0.9 (1.2)	1.1 (1.4)	1.5 (1.7)	0.2 (0.1, 0.4)	0.6 (0.2, 1.0)
Baseline Glucose-Corrected Sodium (mEq/L)	140.4 (4.8)	141.8 (5.3)	143.1 (6.0)	1.4 (0.6, 2.1)	2.7 (1.4, 4.1)
Baseline Bicarbonate (mEq/L)	9.4 (3.1)	8.6 (3.2)	8.3 (3.1)	−0.8 (−1.3, −0.3)	−1.1 (−1.8, −0.4)
Baseline pH	7.18 (0.09)	7.15 (0.10)	7.14 (0.11)	−0.03 (−0.05, −0.02)	−0.04 (−0.07, −0.02)
Baseline Glucose (mg/dL)	498 (146)	518 (169)	553 (166)	20 (−3, 43)	55 (17, 93)
Baseline pCO_2 (mm Hg)	26.4 (6.9)	26.3 (6.8)	26.5 (9.4)	−0.1 (−1.1, 0.9)	0.1 (−2.1, 2.3)
Baseline Anion Gap (mEq/L)	30.9 (5.8)	33.1 (5.9)	33.0 (6.6)	2.2 (1.3, 3.1)	2.1 (0.5, 3.7)
Baseline Heart Rate z-score‡	2.9 (1.7)	3.1 (1.8)	3.4 (1.9)	0.2 (−0.1, 0.5)	0.5 (−0.0, 0.9)
Baseline Systolic Blood Pressure z-score‡	1.3 (1.3)	1.2 (1.2)	1.7 (1.2)	−0.1 (−0.3, 0.1)	0.4 (0.1, 0.7)
Baseline Diastolic Blood Pressure z-score‡	0.9 (1.1)	0.9 (1.0)	1.4 (1.0)	0.0 (−0.1, 0.2)	0.5 (0.3, 0.8)
Capillary refill time evaluated at ED presentation					
Not Documented	14 (3.7%)	12 (3.5%)	3 (3.4%)	−0.2% (−2.9, 2.5)	−0.3% (−4.5, 3.9)
< 2 seconds	224 (59.1%)	177 (51.6%)	38 (42.7%)	−7.5% (−14.7, −0.3)	−16.4% (−27.8, −5.0)
2–5 seconds	138 (36.4%)	152 (44.3%)	46 (51.7%)	7.9% (0.8, 15.1)	15.3% (3.8, 26.7)
> 5 seconds	3 (0.8%)	2 (0.6%)	2 (2.2%)	−0.2% (−1.4, 1.0)	1.5% (−1.8, 4.7)
ED Evaluation GCS Score					
12	2 (0.5%)	1 (0.3%)	1 (1.1%)	−0.2% (−1.2, 0.7)	0.6% (−1.7, 2.9)
13	1 (0.3%)	8 (2.3%)	3 (3.4%)	2.1% (0.4, 3.7)	3.1% (−0.7, 6.9)
14	15 (4.0%)	22 (6.4%)	8 (9.0%)	2.5% (−0.8, 5.7)	5.0% (−1.2, 11.3)
15	361 (95.3%)	312 (91.0%)	77 (86.5%)	−4.3% (−8.0, −0.6)	−8.7% (−16.1, −1.3)
Weight was measured prior to initial IV treatment	325 (85.8%)	272 (79.3%)	70 (78.7%)	−6.5% (−12.0, −0.9)	−7.1% (−16.3, 2.1)
Initial weight z-score adjusted for sex and age‡	0.2 (1.1)	−0.2 (1.3)	−0.8 (1.0)	−0.5 (−0.6, −0.3)	−1.0 (−1.2, −0.7)
Discharge weight z-score adjusted for sex and age‡	0.4 (1.1)	0.2 (1.2)	0.1 (0.9)	−0.2 (−0.4, −0.0)	−0.3 (−0.5, −0.1)
Dehydration severity (% change in body weight from admission to discharge)	2.9 (1.4)	7.1 (1.4)	12.7 (3.5)	4.2 (4.0, 4.4)	9.9 (9.1, 10.6)

BUN=blood urea nitrogen; ED=emergency department; GCS=Glasgow Coma Scale

†Number of DKA Episodes with missing values were as follows for mild, moderate, and severe dehydration categories respectively: Baseline BUN, 22, 20, 9; Baseline Creatinine, 22, 20, 10; Baseline Glucose-Corrected Sodium, 13, 7, 3; Baseline Bicarbonate, 10, 7, 2; Baseline pH, 16, 17, 7;

Baseline pCO_2, 17, 18, 7; Baseline Anion Gap, 29, 29, 9; Baseline Heart Rate z-score, 48, 59, 11; Baseline Systolic and Diastolic Blood Pressure z-scores, 51, 65, 11.

[≠]Adjusted for age and sex using reference norms; blood pressure additionally adjusted for height when available.

Table 1a.

(online only) Characteristics of the included and excluded DKA episodes. Mean (SD) or N (%).[†]

	Included (N = 811)	Excluded (N = 578)	Difference (95% CI)
Age (years)	11.7 (3.9)	11.5 (4.3)	−0.3 (−0.7, 0.2)
Sex: Male	366 (45.1%)	284 (49.1%)	4.0% (−1.3, 9.3)
New onset	391 (48.2%)	265 (45.8%)	−2.4% (−7.7, 3.0)
Baseline BUN (mg/dL)	16.7 (7.0)	17.9 (8.7)	1.3 (0.4, 2.1)
Baseline Creatinine z-score	1.0 (1.4)	1.3 (1.7)	0.2 (0.1, 0.4)
Baseline Glucose-Corrected Sodium (mEq/L)	141.3 (5.2)	140.7 (5.2)	−0.5 (−1.1, 0.0)
Baseline Bicarbonate (mEq/L)	8.9 (3.2)	8.9 (3.3)	0.0 (−0.4, 0.3)
Baseline pH	7.16 (0.10)	7.16 (0.11)	−0.01 (−0.02, 0.01)
Baseline Glucose (mg/dL)	513 (159)	535 (154)	22 (5, 39)
Baseline pCO_2 (mm Hg)	26.4 (7.1)	25.6 (7.6)	−0.8 (−1.6, −0.0)
Baseline Anion Gap (mEq/L)	32.1 (6.0)	32.1 (6.2)	0.0 (−0.7, 0.7)
Baseline Heart Rate z-score[‡]	3.1 (1.8)	3.1 (1.8)	0.1 (−0.1, 0.3)
Baseline Systolic Blood Pressure z-score[‡]	1.3 (1.3)	1.3 (1.4)	0.0 (−0.2, 0.1)
Baseline Diastolic Blood Pressure z-score[‡]	0.9 (1.1)	1.0 (1.1)	0.0 (−0.1, 0.1)
Capillary refill time evaluated at ED presentation			
Not Documented	29 (3.6%)	31 (5.4%)	1.8% (−0.5, 4.0)
< 2 seconds	439 (54.1%)	301 (52.1%)	−2.1% (−7.4, 3.3)
2–5 seconds	336 (41.4%)	239 (41.3%)	−0.1% (−5.3, 5.2)
> 5 seconds	7 (0.9%)	7 (1.2%)	0.3% (−0.7, 1.4)
ED Evaluation GCS 14 or lower	61 (7.5%)	80 (13.8%)	6.3% (3.0, 9.7)
Weight was measured prior to initial IV treatment	667 (82.2%)	477 (82.5%)	0.3% (−3.8, 4.3)
Initial weight z-score adjusted for sex and age[‡]	−0.1 (1.2)	−0.1 (1.3)	0.0 (−0.1, 0.2)
Discharge weight z-score adjusted for sex and age[‡]	0.3 (1.1)	0.2 (1.2)	−0.1 (−0.2, 0.1)
Dehydration severity (% change in body weight from admission to discharge)	5.7 (3.6)	4.5 (4.4)	−1.3 (−1.8, −0.7)

[†]Number of DKA Episodes with missing values were as follows for Included, Excluded respectively: BUN 51, 27; Creatinine 52, 30; Glucose-Corrected Sodium 23, 13; Bicarbonate 19, 12; pH 40, 15; pCO_2 42, 19; Anion Gap 67, 51; Heart Rate 118, 64; Blood Pressure 127, 76, discharge weight 0, 261; dehydration severity 0, 261.

[‡]Adjusted for age and sex using reference norms; blood pressure additionally adjusted for height when available.

Table 2.

Multivariable multinomial regression models predicting dehydration severity based on characteristics at presentation *

	Odds-Ratios (95% Confidence Intervals) †			
	Partially Adjusted Models		Final Adjusted Model	
	Moderate vs Mild	Severe vs Mild	Moderate vs Mild	Severe vs Mild
Clinical Criteria				
New Onset (vs. previously diagnosed) ‡	**1.43 (1.03, 1.99)**	**2.04 (1.21, 3.46)**	**1.86 (1.11, 3.11)**	**2.63 (1.18, 5.83)**
Diastolic Blood Pressure (z-score) ‖	1.02 (0.87, 1.20)	**1.49 (1.15, 1.92)**	1.09 (0.86, 1.37)	**1.74 (1.18, 2.58)**
Capillary refill time ≥ 2 seconds (vs. <2)	**1.40 (1.04, 1.90)**	**2.05 (1.27, 3.32)**	1.01 (0.67, 1.51)	1.42 (0.74, 2.73)
Sex: Male (vs. Female) ‡	1.22 (0.91, 1.64)	**1.72 (1.08, 2.75)**	1.05 (0.72, 1.54)	1.25 (0.67, 2.32)
Systolic Blood Pressure (z-score) ‖	0.94 (0.83, 1.07)	**1.24 (1.02, 1.51)**	**0.82 (0.68, 0.99)**	0.91 (0.67, 1.24)
Heart Rate (Z-score) ‖	1.09 (0.99, 1.20)	**1.32 (1.14, 1.54)**	0.95 (0.83, 1.09)	1.08 (0.87, 1.34)
Age (years) ‡	1.03 (0.98, 1.07)	0.96 (0.90, 1.02)	1.04 (0.98, 1.10)	0.98 (0.90, 1.08)
Laboratory Criteria				
pH (0.1 units)	**0.67 (0.57, 0.79)**	**0.56 (0.44, 0.72)**	**0.69 (0.55, 0.88)**	0.81 (0.56, 1.16)
Creatinine(z-score) ‖	**1.22 (1.08, 1.39)**	**1.53 (1.28, 1.83)**	1.11 (0.91, 1.35)	1.15 (0.87, 1.53)
BUN (mg/dL)	**1.04 (1.01, 1.07)**	**1.07 (1.04, 1.11)**	1.03 (0.99, 1.07)	**1.07 (1.01, 1.14)**
Glucose-corrected Sodium (mEq/L)	**1.06 (1.03, 1.09)**	**1.11 (1.06, 1.16)**	1.02 (0.98, 1.07)	1.06 (0.99, 1.13)
Glucose (per 100 mg/dL increase)	1.09 (0.99, 1.21)	**1.20 (1.05, 1.38)**	0.96 (0.83, 1.10)	0.96 (0.79, 1.17)
Anion Gap (mEq/L)	**1.08 (1.05, 1.11)**	**1.09 (1.04, 1.14)**	**1.05 (1.01, 1.10)**	1.03 (0.96, 1.09)
pCO_2 (mm Hg)	1.00 (0.98, 1.02)	1.01 (0.98, 1.05)	1.00 (0.97, 1.03)	1.00 (0.96, 1.05)
Bicarbonate (mEq/L)	**0.92 (0.88, 0.97)**	**0.89 (0.82, 0.96)**	‡	‡

BUN=blood urea nitrogen

* Complete data were available for N=556 of the 811 visits and were included in the final adjusted model.

† Odds ratios are estimating the change in odds of moderate or severe dehydration versus mild dehydration based on a one- unit change in the predictor except where indicated. All predictors were measured at baseline prior to treatment initiation. Clinical and laboratory criteria are sorted separately by descending absolute log odds ratio comparing severe vs. mild dehydration in the final adjusted model.

‡ Age, sex and new onset of diabetes were included in partially adjusted models. Partially adjusted results for age, sex and new onset are from a multivariable model with those three variables. The final adjusted model included all variables shown; bicarbonate was excluded due to correlation with pH.

‖ Z-scores were calculated as (observed –expected)/standard deviation, where a 1 unit change is equal to a 1 standard deviation change. Expected mean diastolic blood pressure values range from 35 to 77 mm Hg depending on age, sex and height, with an assumed standard deviation ranging from 11.0 to 11.6; expected systolic blood pressure values range from 78 to 127 mm Hg depending on age, sex and height, with an assumed standard deviation ranging from 10.5 to 10.7; expected heart rate values range from 69 to 127 beats/min depending on age and sex, with an assumed standard deviation of 12; expected creatinine values range 0.26 mg/dL for the youngest patients to 0.6 mg/dL for children 14 years old and older, with an assumed standard deviation of 0.2143.

Table 2a.

Multivariable multinomial regression models predicting dehydration severity based on characteristics at presentation, including only those DKA episodes for whom weight was measured prior to initial IV treatment. *

	Odds-Ratios (95% Confidence Intervals) †			
	Partially Adjusted Models		Final Adjusted Model	
	Moderate vs Mild	Severe vs Mild	Moderate vs Mild	Severe vs Mild
Clinical Criteria				
New Onset (vs. previously diagnosed) ‡	1.34 (0.94, 1.92)	**1.87 (1.04, 3.36)**	**1.76 (1.00, 3.10)**	**2.68 (1.04, 6.87)**
Diastolic Blood Pressure (z-score) ‖	0.98 (0.82, 1.17)	**1.49 (1.12, 1.98)**	1.01 (0.78, 1.31)	**1.96 (1.23, 3.14)**
Capillary refill time ≥ 2 seconds (vs. <2)	1.33 (0.95, 1.85)	**1.86 (1.09, 3.18)**	0.83 (0.54, 1.28)	1.48 (0.70, 3.10)
Systolic Blood Pressure (z-score) ‖	0.91 (0.78, 1.04)	1.10 (0.88, 1.38)	0.85 (0.69, 1.03)	0.80 (0.55, 1.16)
Sex: Male (vs. Female) ‡	1.09 (0.78, 1.51)	**1.73 (1.03, 2.93)**	0.87 (0.58, 1.32)	1.13 (0.55, 2.33)
Heart Rate (z-score) ‖	1.09 (0.98, 1.21)	**1.33 (1.12, 1.58)**	0.99 (0.86, 1.15)	1.11 (0.86, 1.43)
Age (years) ‡	1.02 (0.98, 1.07)	0.95 (0.89, 1.02)	1.03 (0.97, 1.10)	0.99 (0.89, 1.10)
Laboratory Criteria				
Glucose-corrected Sodium (mEq/L)	**1.08 (1.04, 1.12)**	**1.15 (1.09, 1.21)**	1.04 (0.99, 1.10)	**1.12 (1.03, 1.21)**
pH (0.1 units)	**0.69 (0.57, 0.82)**	**0.62 (0.47, 0.82)**	**0.74 (0.57, 0.96)**	1.11 (0.70, 1.74)
BUN (mg/dL)	1.03 (1.00, 1.06)	**1.07 (1.02, 1.12)**	1.02 (0.97, 1.06)	**1.09 (1.01, 1.16)**
Creatinine(z-score) ‖	**1.28 (1.09, 1.50)**	**1.57 (1.24, 1.99)**	1.07 (0.86, 1.34)	1.08 (0.74, 1.57)
Glucose (per 100 mg/dL increase)	1.09 (0.97, 1.21)	**1.19 (1.02, 1.40)**	0.91 (0.78, 1.06)	0.95 (0.75, 1.20)
pCO_2 (mm Hg)	0.99 (0.97, 1.02)	0.99 (0.95, 1.03)	1.00 (0.96, 1.03)	0.96 (0.90, 1.02)
Anion Gap (mEq/L)	**1.09 (1.06, 1.13)**	**1.11 (1.06, 1.17)**	**1.06 (1.02, 1.11)**	1.04 (0.96, 1.12)
Bicarbonate (mEq/L)	**0.89 (0.84, 0.94)**	**0.90 (0.82, 0.99)**	‡	‡

BUN=blood urea nitrogen

*Complete data were available for 476 of 667 visits and were included in the final adjusted model.

†Odds ratios are estimating the change in odds of moderate or severe dehydration versus mild dehydration based on a one- unit change in the predictor except where indicated. All predictors were measured at baseline prior to treatment initiation. Clinical and laboratory criteria are sorted separately by descending absolute log odds ratio comparing severe vs. mild dehydration in the final adjusted model.

‡Age, sex and new onset of diabetes were included in partially adjusted models. Partially adjusted results for age, sex and new onset are from a multivariable model with those three variables. The final adjusted model included all variables shown; bicarbonate was excluded due to correlation with pH

‖Z-scores were calculated as (observed –expected)/standard deviation, where a 1 unit change is equal to a 1 standard deviation change. Expected mean diastolic blood pressure values range from 35 to 77 mm Hg depending on age, sex and height, with an assumed standard deviation ranging from 11.0 to 11.6; expected systolic blood pressure values range from 78 to 127 mm Hg depending on age, sex and height, with an assumed standard deviation ranging from 10.5 to 10.7; expected heart rate values range from 69 to 127 beats/min depending on age and sex, with an assumed standard deviation of 12; expected creatinine values range 0.26 mg/dL for the youngest patients to 0.6 mg/dL for children 14 years old and older, with an assumed standard deviation of 0.2143.

Table 3.

Treatment received and clinical outcomes by dehydration severity calculated as the percent change in body weight from admission to discharge [*]

Measures of treatment received and outcomes	Mild (0-<5%) (N = 379)	Moderate (5-<10%) (N = 343)	Severe (≥10%) (N = 89)	Difference Between Moderate & Mild (95% CI)	Difference Between Severe & Mild (95% CI)
Time to transition to subcutaneous insulin (hours): Mean (SD)[†]	12.5 (6.4)	14.4 (6.1)	14.2 (6.0)	1.9 (0.9, 2.8)	1.7 (0.3, 3.1)
Hospital length of stay (hours) for new onset patients: Mean (SD)	55.2 (19.6)	60.9 (18.2)	64.6 (16.3)	5.7 (1.7, 9.8)	9.4 (4.1, 14.7)
Hospital length of stay (hours) for previously diagnosed patients: Mean (SD)	32.7 (16.4)	42.2 (18.0)	48.7 (19.7)	9.5 (6.0, 13.0)	16.0 (8.6, 23.4)
Mental status decline (Confirmed GCS score drop to <14)[‡]	3 (0.8%)	7 (2.1%)	3 (3.5%)	1.3% (−0.5, 3.0)	2.7% (−1.3, 6.7)
Received more than the prescribed IV Bolus amount per assigned FLUID protocol	50 (13.2%)	60 (17.5%)	12 (13.5%)	4.3% (−1.0, 9.6)	0.3% (−7.6, 8.2)
Received more than the prescribed fluid amount per assigned FLUID protocol[§]	123 (32.5%)	141 (41.1%)	38 (42.7%)	8.8% (1.8, 15.9)	10.2% (−1.2, 21.5)
Volume of additional fluid received (ml/kg) per assigned FLUID protocol: Mean (SD) [‖]	6.3 (8.8)	6.0 (7.2)	6.8 (8.1)	−0.3 (−2.3, 1.6)	0.5 (−2.6, 3.5)

GCS, Glasgow Coma Scale

[*] Dehydration Severity Scale: Mild (0-<5%), Moderate (5-<10%), Severe (≥ 10%)

[†] Missing for 5 participants (2 mildly dehydrated, 1 moderately dehydrated, 2 severely dehydrated)

[‡] Restricted to participants with GCS score ≥14 at study enrollment (376 mildly dehydrated, 338 moderately dehydrated, 86 severely dehydrated)

[§] Missing data for 3 participants (1 mildly dehydrated, 2 moderately dehydrated).

[‖] Restricted to participants who received more than the prescribed FLUID protocol amount.