Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kuppermann N, Ghetti S, Schunk JE, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. N Engl J Med 2018;378:2275-87. DOI: 10.1056/NEJMoa1716816

Supplementary Appendix

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

The PECARN DKA FLUID Study

Supplemental Appendix

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We acknowledge the efforts of the following individuals participating in PECARN at the time this study was endorsed.

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Methods and Instruments

Power and Sample Size

The primary outcome was binary: whether GCS drops below 14. Each factor in the randomized arms (rate of rehydration and sodium content in the fluid) was tested separately at a 0.025 level, using a Bonferroni correction. The null and alternative hypotheses, for example, for rate of rehydration were, respectively, H0: pA = pB and H1: pA ≠ pB, where pA and pB are, respectively, the true probabilities of developing abnormal mental status under rapid and slow rehydration.

Based on previous data, we estimated that, overall, approximately 15% of the population of interest would develop abnormal mental status during a DKA episode. This study had four arms with many possible different combinations of outcome rates. For the purpose of determining the study sample size, we assumed a rate of 20% as the higher outcome rate of the two levels considered in either test. The study team decided that a 5% difference (i.e., a 15% outcome rate at the other level of the factor being tested) was small enough to be clinically unimportant. A difference of 7.5% was therefore determined to be the minimal clinically-important difference.

Using these hypothesized outcome rates and a power of 90% (0.1 Type II error rate), yielded a required total sample size of approximately 1200 patients. Assuming up to 5% non-adherence to assigned treatment, we increased the sample size to 1200/0.952, or approximately 1330. Making a small, 2% adjustment for O'Brien-Fleming interim monitoring brought the required number up to 1360. This is the number of subject encounters that was the target for the primary analysis. During the time required to enroll 1360 subjects with baseline GCS scores of

14-15, we estimated that up to 150 subjects with baseline GCS scores of 13 or lower might also be enrolled, although these were not included in the primary analysis.

Sensitivity Analysis to Assess Impact of Patients Lost to Follow-Up for Neurocognitive Testing

1,287 DKA episodes occurred in children older than 3 years who met criteria for follow-up neurocognitive testing. In 387 (30.1%) episodes, patients were lost to follow-up or declined to return for neurocognitive testing. Lack of follow-up was mainly due to scheduling issues (e.g. family unable to come in within the specified period) or inability to contact the family (e.g. incorrect phone numbers listed, family did not return calls). In a sensitivity analysis, we found that a shift of more than 2/3 of a standard deviation in outcome scores among patients with incomplete follow-up in one treatment group would indicate a significant treatment effect. A shift of that size among incomplete follow-up patients in one arm and not the others, however, is implausible, given that there were no significant differences among those with complete follow-up.

Description of Instruments Used For Cognitive Assessments.

The Glasgow Coma Scale (GCS) Score is a measure of the state of consciousness of a patient based on eye, motor and verbal criteria. Scores range from 3 to 15 with lower scores indicating more depressed levels of consciousness.

The Color and the Spatial Memory tasks, evaluating long-term memory of items in association with the correct Color Background or Spatial location, results in scores ranging from 0 to 1 with higher scores indicating better memory.

The Wechsler Abbreviated Scale of Intelligence (WASI) yields scores ranging from 40 to 160, with higher numbers indicating higher intelligence quotient (IQ)

The Digit-Span Forward and Backward task, evaluating short-term and working memory, each yields scores varying from 0 to 16, with higher numbers indicating better shorter-term and working memory.

Supplemental Figures

Figure S1. Compliance to Assigned Fluid Rate

The two curves represent the calculated weight-based fluid regimen per study arm for the two assigned fluid rates. The y-axis represents the fluid rate in ml/kg/hr and the x-axis patient weight in kg. The blue circles represent patients on the fast arms and the red squares represent patients on the slow arms. Patients could diverge above the calculated protocol lines by extra fluid boluses (at the discretion of the treating physician) and below the protocol lines by less-than-assigned fluid rates, or time delays in fluid administration.

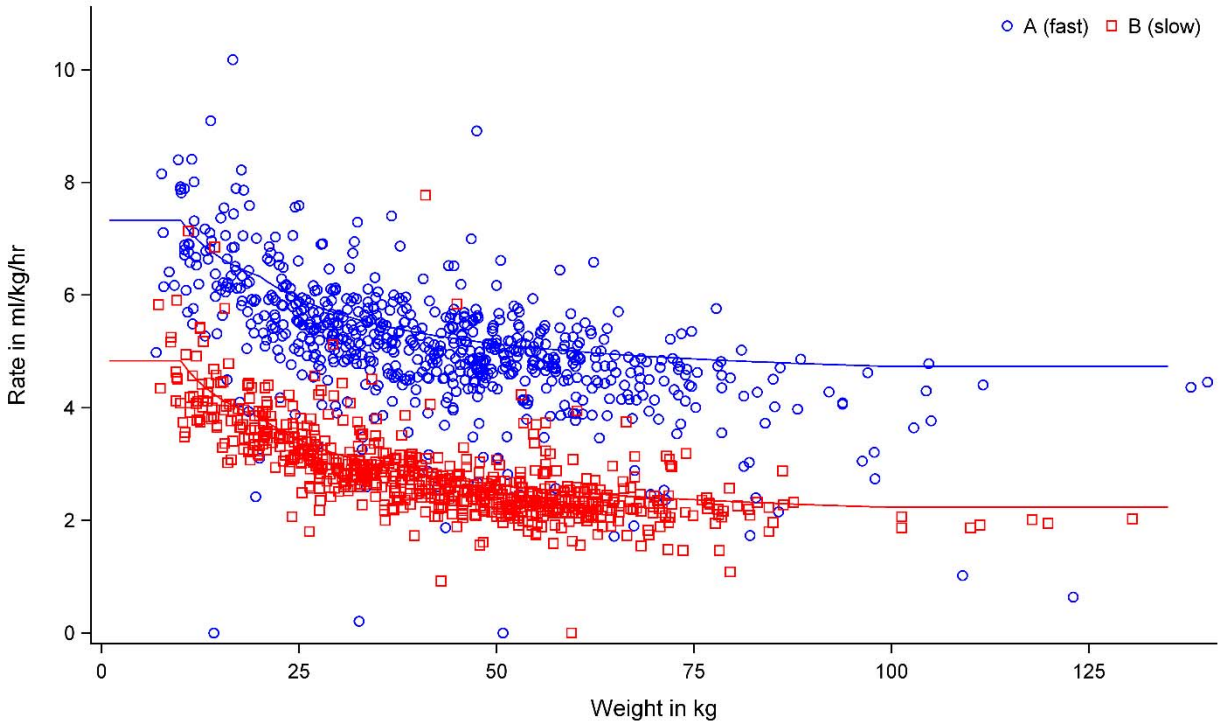


Figure S2. Compliance to Assigned Fluid Sodium Content

The curves represent adherence to the NaCl concentration assignment. Each subject encounter is shown on the x-axis and is represented by up-to 3 points on the y-axis (0.9% NaCl, 0.45% NaCl, and Other fluid) which add to 100%. Each set of points represents the types of fluid a patient received over the first 12-hours of treatment. Initial 0.9% NaCl boluses are not included in these calculations; however, additional boluses administered later in treatment are included, accounting for the increased frequency of 0.9% NaCl use in the 0.45% NaCl arms. Subject encounters are sorted according to compliance to assigned protocol. Those assigned 0.45% NaCl are shown in the top figure. Those assigned 0.9% NaCl are shown in the bottom figure.

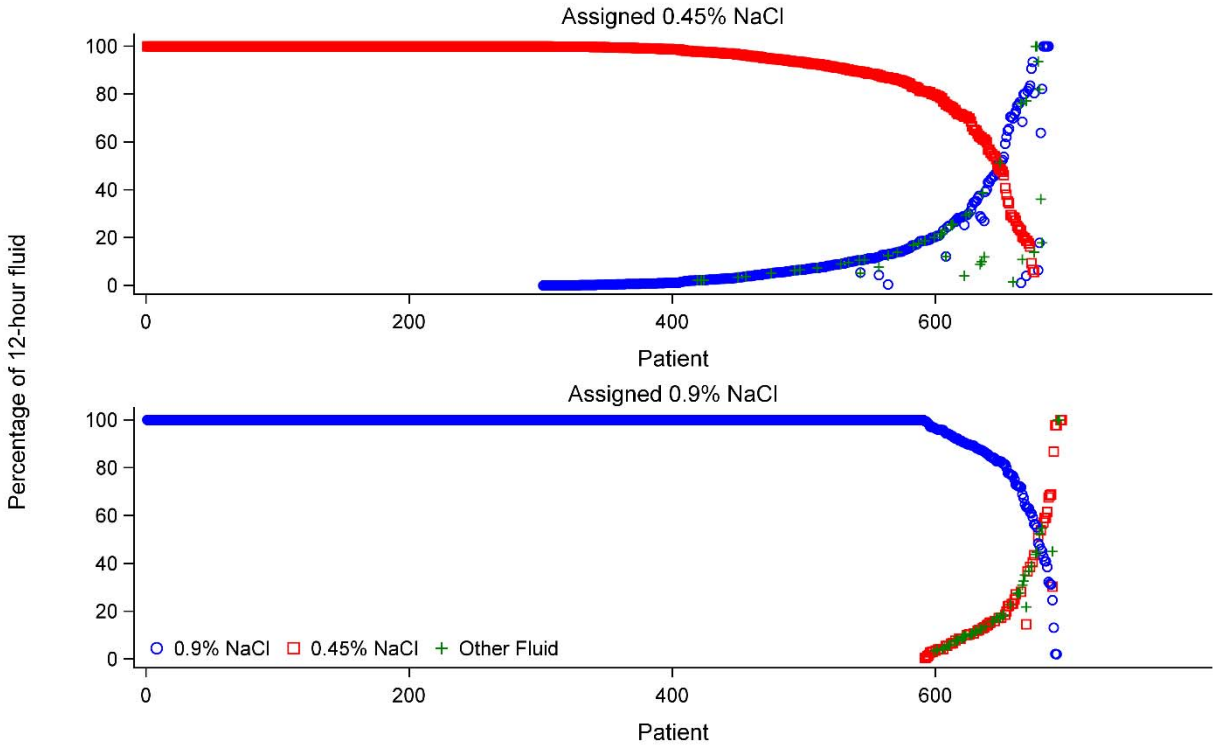
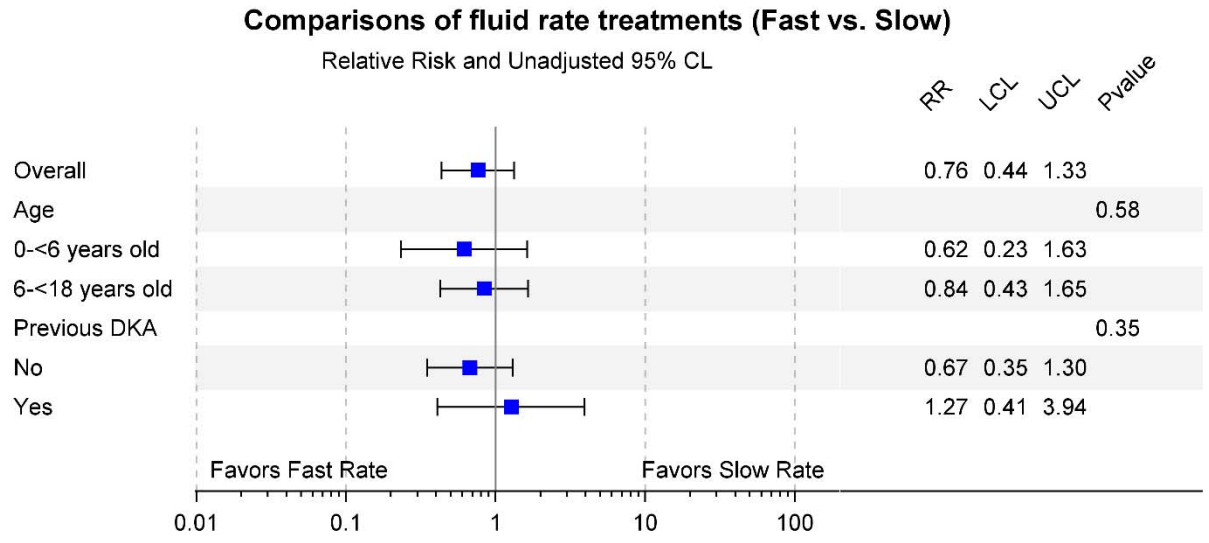
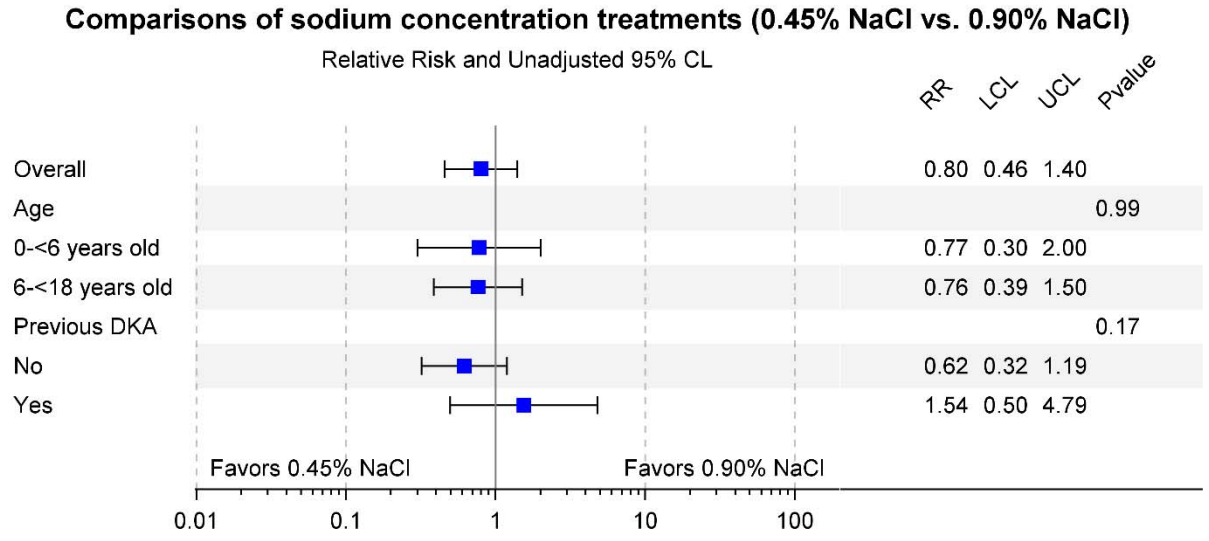


Figure S3. Relative Risk of Confirmed GCS Decline To <14 for Pre-Specified Subgroups

Relative Risks (RR), Upper (UCL) and Lower (LCL) Unadjusted 95% Confidence Limits are shown. P-value is from a logistic regression model testing for differential treatment effects between subgroups. Site is included in the overall model. The comparison of fluid rate (top figure) is shown separately from the comparison of fluid sodium concentration (bottom figure).





Supplemental Tables

Table S1. Subject Encounters Enrolled and GCS Outcome Rates by Enrolling Emergency Departments

Emergency Department*	Randomized and Eligible for GCS outcome	Confirmed GCS Decline to < 14	Treatment Arm†			
			Fast 0.45% NaCl	Fast 0.9% NaCl	Slow 0.45% NaCl	Slow 0.9% NaCl
A	239	5 (2%)	2/60	2/61	0/60	1/58
B	189	7 (4%)	1/47	0/48	4/47	2/47
C	183	10 (5%)	2/45	2/46	3/46	3/46
D	113	3 (3%)	0/27	0/28	2/29	1/29
E	109	1 (1%)	0/27	0/28	1/27	0/27
F	99	2 (2%)	0/25	0/25	0/24	2/25
G	84	5 (6%)	2/20	1/21	0/21	2/22
H	83	0 (0%)	0/21	0/20	0/21	0/21
I	76	9 (12%)	2/20	3/18	1/18	3/20
J	60	0 (0%)	0/15	0/15	0/15	0/15
K	56	2 (4%)	1/14	1/15	0/13	0/14
L	47	1 (2%)	0/11	0/12	0/12	1/12
M	23	3 (13%)	0/5	2/8	0/5	1/5

*Emergency departments are ordered according to total enrollment.

†The number with the outcome/number enrolled is shown for each treatment arm.

Table S2. Patients Who Developed Clinically-Apparent Brain Injury: Clinical and Biochemical Features At Time of Emergency Department Presentation, Treatment Administered and Outcome

Study Arm	Age (years)	Glucose mg/dL (mmol/L)	pH	pCO_2	Na mmol/L	BUN mg/dL (mmol/L)	GCS+	Mannitol	3% Saline	Intubated	Outcome
B2	16	693 (38.5)	6.92	22	140	15 (5.4)	14	x			normal
B2	9	524 (29.1)	6.84	16	140	14 (5.0)	13	x			normal
A2	12	1377 (76.4)	6.96	17	107	36 (12.9)	15	x			normal
B1	13	434 (24.1)	7.01	19	127	26 (9.3)	14		x		normal
A1	5	750 (41.6)	6.95	20	128	19 (6.8)	13	x	x	x	death*
A1	4	350 (19.4)	7.30	23	139	23 (8.2)	15	x	x		normal
B1	15	699 (38.8)	7.12	12	131	30 (10.7)	15	x			normal
B1	8	1634 (90.7)	7.19	30	123	24 (8.6)	15	x			normal
B2	11	473 (26.3)	7.08	18	127	14 (5.0)	15		x		normal
B1	8	1410 (78.3)	6.99	21	130	23 (8.2)	14	x	x		normal
A2	3	1000 (55.5)	†	†	137	39 (13.9)	14	x			normal
B1	10	687 (38.1)	6.99	27	136	26 (9.3)	14	x			normal

* All children recovered to baseline mental status with the exception of one patient who died.

A detailed description of the one patient death is provided here: The patient was a 5 year-old girl who presented with a GCS score of 14. She presented with poor peripheral perfusion, weak peripheral pulses and delayed capillary refill time. She received a 20 cc/kg bolus of 0.9% NaCl prior to study enrollment. At the time of randomization, her GCS score was 13. At hour 2 of treatment, she was randomized to arm A1 and began the study infusion rate at that time. There were slight delays in obtaining the study fluid (0.45% NaCl with potassium salts) which began at hour 3.5. Approximately 30 minutes later, her GCS score was noted to be 9. At that time, her glucose level was 627mg/dL (34.8 mmol/L) (rate of decline since treatment initiation: 31 mg/dL/hr (1.7 mmol/L/hr)) and serum sodium was 135 mmol/L. At hour 7, her GCS score was 14 but again declined to scores of 9 to 10. From hour 4 until hour 12 of treatment, glucose levels declined from 627 to 226 mg/dL (34.8 to 12.5 mmol/L) (rate of decline 50 mg/dL/hr (2.8 mmol/L/hr)), and remained between 220-280 mg/dL (12.2-15.5 mmol/L) while still on study protocol, until hour 15. Sodium levels between hour 4 and hour 15 were measured every 2 hours and varied between 131-138 mmol/L. At hour 15, the patient was noted to have left arm flexion with clonic movement followed by body stiffening lasting 30 seconds along with decline in her GCS score to 3. She was emergently intubated secondary to hypopnea and altered mental status. She was treated with mannitol and hypertonic saline without significant improvement in her mental status. After intubation, she was hypotensive and had minimally reactive and dilated pupils. A head CT scan showed diffuse cerebral edema with loss of gray-white matter differentiation. Brain death was declared on day 3.

† pH and pCO_2 were not measured at ED presentation. Serum bicarbonate concentration at presentation was 7 mmol/L.

+ GCS at time of randomization

Table S3. Additional Analyses of GCS Outcomes

	A1: Fast 0.45% NaCl (N = 344)	A2: Fast 0.9% NaCl (N = 351)	B1: Slow 0.45% NaCl (N = 345)	B2: Slow 0.9% NaCl (N = 349)	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
Magnitude of GCS Decline (GCS points)					0.62	0.16
0 to 1	325 (94%)	337 (96%)	325 (94%)	327 (94%)		
2 to 3	7 (2%)	10 (3%)	16 (5%)	10 (3%)		
4 or greater	12 (3%)	4 (1%)	4 (1%)	12 (3%)		
Duration GCS <14					0.35	0.72
No GCS scores <14	320 (93%)	329 (94%)	317 (92%)	322 (92%)		
<120 minutes	11 (3%)	13 (4%)	19 (6%)	11 (3%)		
120 minutes or longer	13 (4%)	9 (3%)	9 (3%)	16 (5%)		

Due to the factorial nature of the study, each patient is included in both the rate and concentration comparisons. P-values are from van Elteren tests stratified by NaCl (Fast vs. Slow comparisons), rate (0.45% vs. 0.9% NaCl comparisons) and hospital

Table S4. Mental Status Changes during DKA in High-Risk Subgroups

Table S4A. Patients with Initial pH in the Lowest Quartile of the Study Group (pH <7.10)

Analysis of Confirmed GCS Decline <14	A1: Fast 0.45% NaCl n=63	A2: Fast 0.9% NaCl n=68	B1: Slow 0.45% NaCl n=78	B2: Slow 0.9% NaCl n=73	Fast vs. Slow		0.45% vs. 0.9%	
					Subgroup Interaction P-value	Within Subgroup P-Value	Subgroup Interaction P-value	Within Subgroup P-Value
Confirmed GCS Decline to < 14	4 (6.3%)	7 (10.3%)	7 (9.0%)	11 (15.1%)	0.58	0.31	0.09	0.16
Relative Risk (95% CI)					0.69 (0.34, 1.41)		0.60 (0.30, 1.23)	
Secondary Outcomes	n=69	n=72	n=83	n=79				
Clinically-Apparent Brain Injury	1 (1.4%)	1 (1.4%)	3 (3.6%)	3 (3.8%)	0.87	0.22	0.95	0.97
Digit Span Recall Test: Forward Slope (SE)	0.091 (0.019)	0.090 (0.019)	0.074 (0.017)	0.073 (0.017)	0.84	0.39	0.35	0.98
Digit Span Recall Test: Backward Slope (SE)	0.100 (0.016)	0.099 (0.016)	0.057 (0.015)	0.056 (0.015)	0.01	0.01	0.92	0.94

Statistical analyses are as described in main Table 3 footnote. Subgroup interaction p-values test for a differential treatment effect between the pH <7.10 and pH ≥7.10 subgroups. Within subgroup p-values test for a treatment effect within the pH <7.10 subgroup.

Table S4B. Patients with Initial pCO_2 in the Lowest Quartile of the Study Group (pCO_2 <21 mmHg)

Analysis of Confirmed GCS Decline <14	A1: Fast 0.45% NaCl n=66	A2: Fast 0.90% NaCl n=82	B1: Slow 0.45% NaCl n=79	B2: Slow 0.9% NaCl n=65	Fast vs. Slow		0.45% vs. 0.9%	
					Subgroup Interaction P-value	Within Subgroup P-Value	Subgroup Interaction P-value	Within Subgroup P-Value
Confirmed GCS Decline to < 14	2 (3.0%)	6 (7.3%)	4 (5.1%)	4 (6.2%)	0.54	0.87	0.37	0.31
Relative Risk (95% CI)					0.92 (0.35, 2.44)		0.60 (0.22, 1.64)	
Secondary Outcomes	n=70	n=84	n=82	n=69				
Clinically-Apparent Brain Injury	1 (1.4%)	1 (1.2%)	2 (2.4%)	2 (2.9%)	0.61	0.40	0.28	0.95
Digit Span Recall Test: Forward Slope (SE)	0.119 (0.023)	0.104 (0.022)	0.068 (0.020)	0.052 (0.022)	0.03	0.03	0.33	0.52
Digit Span Recall Test: Backward Slope (SE)	0.092 (0.021)	0.079 (0.020)	0.058 (0.019)	0.045 (0.020)	0.16	0.12	0.32	0.56

Statistical analyses are as described in main Table 3 footnote. Subgroup interaction p-values test for a differential treatment effect between the pCO_2 <21mmHg and pCO_2 ≥21mmHg subgroups. Within subgroup p-values test for a treatment effect within the pCO_2 <21mmHg subgroup.

Table S4C. Patients with Initial Glucose Levels in the Highest Quartile of the Study Group (Glucose > 600 mg/dL (33.3 mmol/L))

Analysis Of Confirmed GCS Decline <14	A1: Fast 0.45% NaCl n=79	A2: Fast 0.9% NaCl n=90	B1: Slow 0.45% NaCl n=66	B2: Slow 0.9% NaCl n=75	Fast vs. Slow		0.45% vs. 0.9%	
					Subgroup Interaction P-value	Within Subgroup P-Value	Subgroup Interaction P-value	Within Subgroup P-Value
Confirmed GCS Decline to < 14	3 (3.8%)	5 (5.6%)	5 (7.6%)	9 (12.0%)	0.16	0.08	0.46	0.31
Relative Risk (95% CI)					0.48 (0.21, 1.10)		0.65 (0.28, 1.50)	
Secondary Outcomes	n=83	n=93	n=69	n=77				
Clinically-Apparent Brain Injury	1 (1.2%)	1 (1.1%)	2 (2.9%)	1 (1.3%)	0.83	0.51	0.83	0.57
Digit Span Recall Test: Forward Slope (SE)	0.079 (0.020)	0.087 (0.020)	0.060 (0.020)	0.068 (0.019)	0.95	0.39	0.45	0.73
Digit Span Recall Test: Backward Slope (SE)	0.075 (0.021)	0.071 (0.020)	0.059 (0.021)	0.056 (0.020)	0.69	0.50	0.62	0.86

Statistical analyses are as described in main Table 3 footnote. Subgroup interaction p-values test for a differential treatment effect between the glucose >600 mg/dL (33.3 mmol/L) and glucose ≤600 mg/dL (33.3 mmol/L) subgroups. Within subgroup p-values test for a treatment effect within the glucose >600 mg/dL (33.3 mmol/L) subgroup.

Table S4D. Patients with Initial BUN Levels in the Highest Quartile of the Study Group (BUN > 21 mg/dL (7.5 mmol/L))

Analysis of Confirmed GCS Decline <14	A1: Fast 0.45% NaCl n=74	A2: Fast 0.9% NaCl n=69	B1: Slow 0.45% NaCl n=73	B2: Slow 0.9% NaCl n=72	Fast vs. Slow		0.45% vs. 0.9%	
					Subgroup Interaction P-value	Within Subgroup P-Value	Subgroup Interaction P-value	Within Subgroup P-Value
Confirmed GCS Decline to < 14	3 (4.1%)	3 (4.3%)	8 (11.0%)	6 (8.3%)	0.16	0.07	0.20	0.69
Relative Risk (95% CI)					0.43 (0.17, 1.10)		1.19 (0.51, 2.76)	
Secondary Outcomes	n=74	n=73	n=77	n=73				
Clinically-Apparent Brain Injury	1 (1.4%)	2 (2.7%)	5 (6.5%)	0 (0.0%)	0.67	0.50	0.13	0.17
Digit Span Recall Test: Forward Slope (SE)	0.046 (0.021)	0.069 (0.020)	0.024 (0.018)	0.046 (0.020)	0.88	0.31	0.20	0.32
Digit Span Recall Test: Backward Slope (SE)	0.025 (0.020)	0.043 (0.019)	0.045 (0.017)	0.063 (0.019)	0.11	0.35	0.54	0.40

Statistical analyses are as described in main Table 3 footnote. Subgroup interaction p-values test for a differential treatment effect between the BUN >21 mg/dL (7.5 mmol/L) and BUN ≤21 mg/dL (7.5 mmol/L) subgroups. Within subgroup p-values test for a treatment effect within the BUN >21 mg/dL (7.5 mmol/L) subgroup.

Table S5. Analysis of Post-Recovery Neurocognitive Outcomes by Treatment Arm

Table S5A. Memory Score and Full Scale IQ Measured at 2-6 Months after Hospitalization

	A1: Fast 0.45% NaCl	A2: Fast 0.9% NaCl	B1: Slow 0.45% NaCl	B2: Slow 0.9% NaCl	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
6 to 18 Years-Old						
Memory Score*	0.60 (0.14) n=175	0.60 (0.14) n=184	0.61 (0.14) n=178	0.60 (0.14) n=176	0.54	0.78
Item Color Rate	0.49 (0.17) n=181	0.50 (0.17) n=188	0.51 (0.17) n=183	0.49 (0.17) n=177	0.86	0.99
Item Space Rate	0.70 (0.18) n=176	0.69 (0.19) n=191	0.71 (0.17) n=181	0.71 (0.18) n=180	0.63	0.68
Full Scale IQ	102 (12) n=187	102 (13) n=201	102 (13) n=191	103 (13) n=189	0.50	0.64
3 to 5 Years-Old						
Memory Score*	0.43 (0.09) n=6	0.51 (0.11) n=9	0.41 (0.16) n=7	0.47 (0.17) n=5	0.75	0.23
Item Color Rate	0.30 (0.11) n=7	0.44 (0.21) n=11	0.39 (0.14) n=9	0.36 (0.16) n=6	0.85	0.39
Item Space Rate	0.57 (0.21) n=7	0.57 (0.12) n=10	0.43 (0.24) n=7	0.57 (0.24) n=5	0.32	0.60
Full Scale IQ	105 (12) n=11	101 (13) n=19	101 (12) n=15	100 (16) n=9	0.49	0.40

Mean (SD): N shown; P-values are from Van Elteren tests stratified by NaCl (for the Fast vs. Slow comparisons), and rate (for the 0.45% vs. 0.9% NaCl comparisons)

*Mean of item color rate and item space rate.

Table S5B. Digit Span Scores Measured at 2-6 Months after Hospitalization

	A1: Fast 0.45% NaCl	A2: Fast 0.9% NaCl	B1: Slow 0.45% NaCl	B2: Slow 0.9% NaCl	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
Forward Digit Span Score	8.17 (0.13) n=206	8.16 (0.12) n=225	8.16 (0.13) n=214	8.15 (0.14) n=201	0.96	0.97
Backward Digit Span Score	6.83 (0.12) n=206	6. 51 (0.13) n=224	6.73 (0.13) n=214	6.92 (0.15) n=201	0.25	0.57

Age-adjusted mean (SE), with a reference age of 12 years-old shown; P-values are from Van Elteren tests stratified by NaCl (for the Fast vs. Slow comparisons), and rate (for the 0.45% vs. 0.9% NaCl comparisons)

Table S6. Mental Status Changes during DKA Treatment: *Per-Protocol Analysis*

	Fast 0.45% NaCl	Fast 0.9% NaCl	Slow 0.45% NaCl	Slow 0.9% NaCl	Fast vs. Slow	0.45% vs. 0.9%
Analysis of confirmed GCS decline <14	n=314	n=311	n=308	n=321	P-value	P-value
Confirmed GCS Decline to < 14	7 (2.2%)	10 (3.2%)	9 (2.9%)	13 (4.0%)	0.39	0.30
Relative Risk (95% CI)	Fast vs. Slow 0.76 (0.40, 1.42)		0.45% vs. 0.9% 0.72 (0.38, 1.35)		Interaction: 1.00	
Secondary Outcomes	n=319	n=316	n=313	n=326		
Clinically Apparent Brain Injury (Adjudicated)	1 (0.3%)	1 (0.3%)	3 (1.0%)	3 (0.9%)	0.16	0.99
Relative Risk (95% CI)	Fast vs. Slow 0.34 (0.07,1.66)		0.45% vs. 0.9% 0.99 (0.25, 3.90)		Interaction: 1.00	
Forward Slope (SE)	0.070 (0.010)	0.054 (0.010)	0.055 (0.010)	0.039 (0.010)	0.14	0.11
Backward Slope (SE)	0.056 (0.009)	0.049 (0.009)	0.049 (0.009)	0.042 (0.009)	0.45	0.46

Statistical analyses are as described in main Table 3 footnote. Patient encounters were excluded when the fluid treatment regimen deviated sufficiently from the assigned protocol that the fluid rate or sodium content was more similar to another protocol arm than to the assigned arm.

Table S7. Post-Recovery Neurocognitive Outcomes Measured 2-6 Months after Hospitalization by Treatment Arm: *Per-Protocol Analysis*

	A1: Fast 0.45% NaCl	A2: Fast 0.9% NaCl	B1: Slow 0.45% NaCl	B2: Slow 0.9% NaCl	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
6 to 18 Years-Old						
Memory Score	170: 0.60 (0.14)	168: 0.59 (0.15)	164: 0.62 (0.14)	163: 0.61 (0.14)	0.18	0.62
Item Color Rate	176: 0.49 (0.17)	171: 0.50 (0.17)	169: 0.51 (0.17)	164: 0.50 (0.17)	0.48	0.98
Item Space Rate	171: 0.70 (0.17)	175: 0.69 (0.19)	167: 0.71 (0.17)	167: 0.72 (0.18)	0.34	0.74
Full Scale IQ	181: 103 (12)	184: 102 (13)	177: 102 (13)	176: 103 (14)	0.82	0.85
3 to 18 Years-Old						
Forward Digit Span Score	198: 8.20 (0.14)	207: 8.18 (0.13)	197: 8.19 (0.14)	188: 8.07 (0.15)	0. 67	0.74
Backward Digit Span Score	198: 6.84 (0.13)	206: 6.52 (0.13)	197: 6.75 (0.14)	188: 6.90 (0.16)	0.32	0.53

Number of patients: Mean (SD) shown for memory score and IQ measures. Number of patients: age-adjusted mean (SE) shown for digit span score measures (reference age of 12). P-values are from Van Elteren tests stratified by NaCl (for the Fast vs. Slow comparisons), and rate (for the 0.45% vs. 0.9% NaCl comparisons). Patient encounters were excluded when the fluid treatment regimen deviated sufficiently from the assigned protocol that the fluid rate or sodium content was more similar to another protocol arm than to the assigned arm.

Table S8. Non-Neurological Adverse Events*

	A1: Fast 0.45% NaCl (n= 344)	A2: Fast 0.9% NaCl (n=351)	B1: Slow 0.45% NaCl (n=345)	B2: Slow 0.9% NaCl (n=349)	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
Hypoglycemia (Glucose<70 mg/dL (3.9 mmol/L))	90 (26.2%)	88 (25.1%)	82 (23.8%)	112 (32.1%)	0.33	0.14
Hypokalemia (Potassium<3.0 mmol/L)	51 (14.8%)	69 (19.7%)	59 (17.1%)	64 (18.3%)	0.81	0.15
Hypopohosphatemia†,‡	188 (54.7%)	209 (59.5%)	176 (51.0%)	199 (57.0%)	0.26	0.03
Hyperchloremic Acidosis§	122 (35.5%)	142 (40.5%)	95 (27.5%)	113 (32.4%)	<0.001	0.04
Hypocalcemia|	133 (38.7%)	173 (49.3%)	96 (27.8%)	130 (37.2%)	<0.001	<0.001
Thrombosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA
Renal Failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	NA
Pancreatitis	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0.98	0.98
Pulmonary Edema	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0.99	0.99
Cardiac Arrhythmia	2 (0.6%)	2 (0.6%)	4 (1.2%)	2 (0.6%)	0.51	0.49

*N (%) shown for all outcomes. P-values are from Mantel-Haenszel tests stratified by NaCl (for the Fast vs. Slow comparisons), rate (for the 0.45% vs. 0.9% NaCl comparisons) and hospital.
†Serum phosphate <4.3 mg/dL (1.4 mmol/L, age <5 yrs), <3.7 mg/dL (1.2mmol/L, age 5 -<14 yrs), <3.5 mg/dL (1.1 mmol/L, age 14-<16 yrs), <3.1 mg/dL (1.0mmol/L, age ≥16 yrs).
‡There were no reports of adverse consequences (rhabdomyolysis, hemolytic anemia) of hypophosphatemia.
§Hyperchloremic acidosis defined as serum bicarbonate below age-based lower limit (age 0-<4 yrs: 18 mmol/L, 4-<6: 19 mmol/L, 6-<8 yrs: 20 mmol/L, >8 yrs: 21 mmol/L) and anion gap < 12, or reported as an adverse event by the treating physician.
| Calcium <8.5 mg/dL (2.13 mmol/L). Twelve patients were treated with calcium supplementation for hypocalcemia (four in arm A1, four in A2, two in B1 and two in B2).

Table S9. Serious Adverse Events

	A1: Fast 0.45% NaCl (N = 342)	A2: Fast 0.9% NaCl (N = 344)	B1: Slow 0.45% NaCl (N = 338)	B2: Slow 0.9% NaCl (N = 347)
Nervous System Disorders	4 (1%)	2 (1%)	8 (2%)	7 (2%)
Metabolism and Nutrition Disorders	1 (0%)	1 (0%)	0 (0%)	3 (1%)
Gastrointestinal Disorders	0 (0%)	1 (0%)	1 (0%)	0 (0%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac Disorders	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatobiliary Disorders	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Infections and Infestations	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Renal and Urinary Disorders	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular Disorders	0 (0%)	0 (0%)	1 (0%)	0 (0%)

The data shown pertain to patient encounters for whom study treatment was initiated (safety population).
36 serious adverse events were experienced by 30 patients.

Table S10. Time to DKA Resolution and Hospital Discharge*

	A1: Fast 0.45% NaCl (n= 344)	A2: Fast 0.9% NaCl (n=351)	B1: Slow 0.45% NaCl (n=345)	B2: Slow 0.9% NaCl (n=349)	Fast vs. Slow P-value	0.45% vs. 0.9% P-value
Time to DKA Resolution† (Hours)	14.0 (10.2 - 18.3)	14.0 (9.8-18.3)	14.9 (9.9-18.6)	13.6 (10.0-18.5)	0.28	0.48
Time to Hospital Discharge (Hours)	46.3 (27.3-66.3)	47.4 (26.6-67.2)	48.6 (28.0-68.8)	46.4 (27.2-69.0)	0.34	0.71

*Median (25th percentile - 75th percentile) shown for all outcomes. P-values are from a Van Elteren test stratified by NaCl (for the Fast vs. Slow comparisons), rate (for the 0.45% vs. 0.9% NaCl comparisons) and hospital.

†Time from randomization until transition to subcutaneous (SC) insulin administration if within 24 hours; time until anion gap ≤12 if transition to SC insulin was after 24 hours; time until transition to SC insulin if anion gap ≤12 not documented.