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Pediatric Diabetic Ketoacidosis, Fluid Therapy and Cerebral Injury: The Design of a Factorial Randomized Controlled Trial

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Abstract

Treatment protocols for pediatric diabetic ketoacidosis (DKA) vary considerably among centers in the United States and worldwide. The optimal protocol for intravenous fluid administration is an area of particular controversy, mainly in regard to possible associations between rates of intravenous fluid infusion and the development of cerebral edema, the most common and most feared complication of DKA in children. Theoretical concerns about associations between osmotic fluid shifts and cerebral edema have prompted recommendations for conservative fluid infusion during DKA. However, recent data suggest that cerebral hypoperfusion may play a role in cerebral

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injury associated with DKA. Currently there are no existing data from prospective clinical trials to determine the optimal fluid treatment protocol for pediatric DKA. The Pediatric Emergency Care Applied Research Network FLUID (Fluid Therapies Under Investigation in DKA) Study is the first prospective randomized trial to evaluate fluid regimens for pediatric DKA. This 13-center nationwide factorial-design study will evaluate the effects of rehydration rate and fluid sodium content on neurological status during DKA treatment, the frequency of clinically-overt CE, and long-term neurocognitive outcomes following DKA.

Background

The optimal treatment for pediatric diabetic ketoacidosis (DKA) has been a topic of debate for decades. Multiple working groups and consensus conferences have been convened to develop guidelines for pediatric DKA treatment. These efforts, however, have been hampered by a lack of high-quality data from randomized controlled trials to guide therapeutic recommendations.[1-3] Intravenous fluid regimens for rehydration of children with DKA have been the main topic of controversy. Consensus statements concerning intravenous (IV) fluid regimens for rehydration of children with DKA have provided broad, general guidelines because data are unavailable to support more precise recommendations. A recent informal poll of 20 hospitals participating in the Pediatric Emergency Care Applied Research Network (PECARN) suggests that substantial variability in DKA management continues to exist (unpublished data), similar to that documented in older published literature.[4] According to currently-used protocols in the pediatric referral centers participating in PECARN, a 40 kg child with DKA could receive IV fluid at rates as high as 215 ml/hr or as low as 114 ml/hr. Similarly, there is disagreement about the optimal sodium content of rehydration fluid with some using 0.45% saline, others 0.9% saline and others using a combination. This substantial treatment variation reflects the lack of evidence to guide management and underscores the need for a definitive randomized controlled trial.

At the center of the controversy surrounding DKA treatment in children are physicians' concerns about possibly causing or exacerbating DKA-related cerebral edema (CE) or cerebral injury with inappropriate intravenous rehydration. Clinically overt and potentially life-threatening CE occurs in only 0.5-1% of DKA episodes, making this entity difficult to study. [5, 6] However, CE that is asymptomatic or associated with only minor mental status disturbances, has been documented to occur in most children with DKA.[7-10] In addition, while it was previously assumed that children who did not develop clinically-overt CE recovered fully, without lasting neurological injury, recent data suggest that this is not the case. DKA episodes without clinically-overt CE have been associated with permanent deficits in memory function.[11] Evidence to guide clinical care of children with DKA is therefore essential not only for the goal of decreasing the rate of clinically-overt, life-threatening CE, but also to reduce the incidence of subclinical CE resulting in neurocognitive dysfunction.

Some investigators hypothesized that CE may result from osmotic shifts caused by rapid IV rehydration.[12-14] As a consequence, many protocols manage DKA in children with conservative fluid therapy. Although this hypothesis is intuitively appealing, data showing clear associations between aggressive fluid therapy and CE are lacking. Instead, recent data suggest that cerebral hypoperfusion and the effects of reperfusion during DKA treatment may play a prominent role in the development of cerebral injury and CE.[6, 15-17] Conservative rehydration protocols could delay reestablishment of normal cerebral perfusion, and could be detrimental, rather than protective. Use of low sodium content fluids may exacerbate this problem by decreasing the volume of fluid retained in the vascular space, while use of isotonic saline may slow repair of intracellular dehydration. Conversely,

more rapid infusion of fluids might increase vasogenic edema associated with cerebral reperfusion, particularly if breakdown of the blood-brain barrier has occurred from ischemia.

The PECARN Fluid Therapies Under Investigation in DKA ("FLUID") study is the first prospective randomized controlled clinical trial to investigate the impact of fluid rehydration regimens on neurological and neurocognitive outcomes in children with DKA. The study will determine the effects of rehydration rate and fluid sodium content on neurological status during DKA treatment, the frequency of clinically-overt CE, and long-term neurocognitive outcomes.

Methods

Overview

The PECARN FLUID study is a factorial-design randomized controlled trial comparing four fluid treatment protocols for children with DKA. Two rates of rehydration will be compared; a more rapid rate, designed to promote faster reperfusion of brain tissue and a slower rate, geared toward more gradual reperfusion. Within each of these two rehydration rate schemes, we will compare two sodium concentrations (0.9% saline or 0.45% saline), although all initial fluid boluses will be with 0.9% saline. The study treatment arms were based on the high and low ends of the range of treatment protocols in current use in PECARN hospitals. We will compare treatment arms using comprehensive assessments for neurological injury including measurements of subtle neurological dysfunction during DKA treatment (in addition to recording the frequency of acute, clinically-overt CE) and measures of long-term neurocognitive function several months after hospital discharge.

Inclusion/exclusion criteria

Children meeting the following criteria will be considered for enrollment:

1. age < 18 years old at enrollment, and
2. diagnosis of DKA (serum glucose or fingerstick glucose concentration >300 mg/dL, and venous pH< 7.25 *or* serum bicarbonate concentration <15 mmol/L.

The following patients will be excluded from the study:

1. Patients with underlying neurological disorders that would affect either mental status testing during DKA treatment or neurocognitive testing after recovery,
2. Patients who present with DKA concomitant with alcohol or drug use, head trauma, meningitis or other conditions that affect neurological function,
3. Patients with DKA transferred to one of the study sites after receiving an IV fluid bolus of more than 10ml/Kg,
4. Patients who have begun DKA treatment prior to being approached for enrollment and have received (a) more than 2 hours of IV fluid infusion at maintenance rates or higher, OR (b) more than 4 hours of DKA treatment with insulin and/or fluids regardless of rate of infusion,
5. Patients who are pregnant.
6. Patients for whom the treating physicians feel a specific fluid or electrolyte regimen is necessary such that patient safety or wellbeing could be compromised by enrollment into the study.

Enrollment and DKA Treatment protocols

Upon arrival, patients will begin standard fluid therapy using an initial IV fluid bolus of 10cc/kg of 0.9% saline. During this initial therapy, study personnel will obtain informed consent. Randomization will ideally occur prior to initial bolus completion. If consent cannot be obtained within this time frame, patients will be treated with the usual DKA protocol for the study site until consent is completed, but not beyond the time frame outlined in the exclusion criteria.

Children will be randomized to one of four treatment protocols (Table 1). In all protocols, initial bolus volumes will be subtracted from the fluid deficit used to calculate the rate of fluid replacement. Because studies show that clinical estimates of percent dehydration in children with DKA are inaccurate,[18, 19] we assigned an assumed fluid deficit to each protocol (Table 1) based on the upper or lower end of the range documented in recent investigations.[18-21]

All 4 protocols are identical in regard to other aspects of DKA treatment. Fluid boluses may be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Potassium replacement is provided using an equal mixture of potassium chloride and potassium phosphate. Insulin treatment begins after the initial IV fluid bolus(es) as a continuous IV infusion of 0.1 units/kg/hour. When the serum glucose concentration declines below approximately 200-300 mg/dL, dextrose is added to the intravenous fluids to maintain serum glucose between 100 and 200 mg/dL.

Glasgow Coma Scale (GCS) scores are evaluated at enrollment. For patients presenting with GCS scores of ≥14, randomization is stratified by clinical center. A separate, balanced randomization will be used for those patients presenting with GCS scores <14, as these patients will not be included in the primary analysis, and present too infrequently to stratify by clinical center. The PECARN Data Coordinating Center has prepared randomization schedules using variable-length permuted blocks to reduce predictability, as the fluid therapy is non-blinded. Assignments are made through the use of an interactive telephone service.

Outcomes

The *primary study outcome* is the occurrence of abnormal GCS (GCS<14) during DKA treatment, a measure previously demonstrated to correlate with DKA-related CE measured by MRI.[8,15] We will evaluate this dichotomous outcome only in children who present to the emergency department with normal GCS scores (GCS scores >14). Subjects who present with GCS < 14 will not be included in the analysis of the primary outcome, but will be included in the analyses of all other study outcomes.

Safety outcomes include the frequency of adverse events (e.g. thromboses, hyperchloremic acidosis and other electrolyte imbalances, renal failure, cardiac arrhythmias resulting in hemodynamic abnormalities) and death.

Secondary study outcomes will include:

1. Forward and backward digit span recall test scores during DKA treatment. These tests will be used to evaluate working memory and are assessed every 4 hours during waking hours.
2. Clinically overt CE during DKA treatment. Development of clinically-overt CE is defined by severe mental status change diagnosed clinically as CE and associated with: endotracheal intubation or administration of either 3% saline or mannitol.

3. Tests of memory 3 months after recovery from DKA. Memory tests will be used to evaluate various memory functions including item recognition and recollection of contextual detail.

IQ test scores 3 months after recovery from DKA will be evaluated as an exploratory outcome.

Data collection

Clinical and demographic data to be recorded are summarized in Table 2. For children 3 years and older, rapid assessment of working memory (digit span recall) is conducted at enrollment.[22-24] Participants are asked to repeat a series of numbers heard aloud, in the same order as spoken (forward digit span), and then are asked to do the same backwards. The forward task measures the ability to maintain information on line, whereas the backward task measures the ability to mentally manipulate information.[25] The examiner increases the number of digits by one unit on each successive trial as long as the child repeats them correctly. The test ends when the child makes a mistake in two sequences of the same span in a row. The digit span recall test is repeated every 4 hours during normal waking hours (7am to 10pm) with new digit sequences presented each time. Digit span recall is not assessed during usual sleep hours because the patients' cooperation during these hours is limited.

If any of the hourly GCS scores fall below 14, repeat GCS assessment is performed 15 minutes later for reassessment and/or confirmation. If the repeat GCS assessment confirms a GCS score below 14, the patient is classified as having abnormal mental status. Abnormal GCS scores are reported to the attending physicians per usual hospital protocol, and suspected CE is treated at the discretion of the attending physician. Patients with abnormal mental status resulting from hypoglycemia during DKA treatment will not be considered to have met the study outcome.

Assessments of GCS scores and digit span testing continue for 24 hours or until resolution of DKA (transition to subcutaneous insulin administration), whichever comes first. Data from previous studies demonstrate that nearly all neurological injuries caused by DKA occur within the first 24 hours of treatment, and the large majority within the first 12 hours.[6] Therefore extending the monitoring period beyond this time is unlikely to be useful. Biochemical data and any adverse events are recorded until hospital discharge.

Additional clinical and biochemical monitoring conforms with the guidelines at each site, which typically follow international guidelines for the management of DKA in children (Table 2).[1, 3] For children whose parents/guardians decline to participate, as well as for those who were eligible but not approached, demographic, clinical and biochemical variables are recorded to assess for enrolment bias

Post-recovery neurocognitive assessment

Patients 3-17 years of age will return 3 months + 4 weeks after recovery from DKA for neurocognitive assessment. Immediately prior to testing, a fingerstick glucose concentration is measured. Neurocognitive testing is rescheduled if children have hypoglycemia (glucose < 70 mg/dL) or hyperglycemia with ketosis.

Patients older than 6 years are evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI).[26] The WASI has been standardized nationally and yields the three traditional IQ scores; Verbal, Performance and Full Scale IQ. In addition, the working memory (digit span) test is repeated. Memory is further tested with a color task and a spatial-position task that evaluate item recognition and recollection of contextual detail.

These tasks were used to collect data in preliminary studies[11] and in other previous research.[27, 28]

Children 3 to 5 years of age undergo a modified version of IQ and memory testing to accommodate the neurocognitive capacities and shorter attention span of younger children. A short form of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III[29]) is used for IQ assessment, including 4 subtests for 3-year-olds (Receptive Vocabulary, Block Design, Information and Object Assembly) and 7 subtests for 4- and 5-year-olds (Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Word Reasoning and Coding).[30, 31] The working memory (digit span) test is repeated, but the color and spatial-position tasks for contextual memory testing are shortened and simplified to accommodate the typical capacities of this age group.

Multiple DKA episodes

Some children may present with DKA more than once during the study period. To avoid excessively restricting the population available, children previously enrolled into the study who present with another episode of DKA remain eligible. Short-term neurological outcomes (i.e. in-hospital) for both DKA episodes will be included in the main analysis. To avoid bias resulting from very frequent enrollment of specific individuals, children are not enrolled in the study more than twice.

Non-DKA comparison group

Neurocognitive data for children enrolled in the study will be compared not only among the four treatment groups, but also to data from 400 children with Type 1 diabetes who have never experienced DKA. These children are recruited from the pediatric diabetes clinics at the participating centers and tested as previously described. These analyses will allow us to better characterize the effects of DKA (regardless of DKA treatment regimen) on neurocognitive function of children with diabetes, and to determine which sub-sets of children are at greatest risk for neurocognitive dysfunction. We will control statistically for differences in variables potentially affecting neurocognitive outcomes, including age, gender, duration of diabetes, socioeconomic status, episodes of severe hypoglycemia and HbA1c.

Statistical Analysis

We will analyze the study data according to the intention-to-treat principle. Additionally, we will perform per-protocol or fluid-received analyses for additional insight. These latter analyses will not replace the intention-to-treat analysis, and the results of the per-protocol analysis will be examined with caution.

For purposes of sample size calculation, the indicator of abnormal GCS score (i.e. GCS score < 14) during DKA treatment was considered the *primary outcome*. The rationale behind this selection of primary outcome was as follows. Severe, clinically-overt CE occurs in fewer than 1% of DKA episodes and therefore a study large enough to have adequate power to detect differences in this outcome would not be feasible. GCS abnormalities, however, are more frequent in children with greater DKA-related CE measured by magnetic resonance imaging,[15] and increasing evidence suggests that DKA-related CE presents as a continuum of severity, from asymptomatic to clinically-overt (see Discussion). It seems reasonable to assume, therefore, that fluid protocols that decrease the frequency of GCS abnormalities are also likely to decrease the likelihood of clinically-overt CE.

Only subjects with baseline GCS scores of 14 or 15 will be included in the primary analysis. A Mantel-Haenszel test, stratified by center and controlling for the other treatment factor,

will be performed for each of the two factors (rate of fluid administration and sodium content of fluids). To control the type I error rate, each factor will be tested at a 0.025 level.

The interaction between fluid rate and sodium content will be tested in an exploratory analysis. Furthermore, two additional analyses of GCS scores will be used: drop in GCS score (difference between baseline and lowest GCS score) and the duration of time for which the GCS score is below 14. These two GCS outcomes will be analyzed using a Van Elteren test, controlling for strata. We will perform exploratory analyses of the GCS score outcomes by assessing the treatment effect after adjustment for covariates. The frequency of clinically-overt CE will be tested using the Mantel-Haenszel test, as described for the primary analysis.

For digit span scores, we will apply longitudinal data analysis methods by assuming a linear mixed-effects model. Time zero will be randomization time. The time-treatment interactions are the quantities of interest, as they represent the change over time due to each treatment. We will additionally evaluate other possible exploratory models, including interactions and non-linear relationships.

The main memory task analysis will focus on the average of the item color association rate and the item space association rate. These scores will be compared using a Van Elteren test, controlling for strata. We will investigate the effects of treatment after adjusting for important covariates in a linear model. The main tests for the three outcomes of forward digit span, backward digit span, and memory score will be subject to Holm's procedure for multiple comparisons. The same analytical approach proposed for memory will be used for the analyses of IQ measures. General linear models will be used to adjust for known age-related differences in measurement error and variance in IQ.[26, 32]

We also plan to determine whether treatment effects are consistent across prospectively defined subgroups. Variables used to define subgroups will include age (younger than 6 years vs. 6 years and older), baseline GCS scores (14 vs 15) and history of previous DKA (possibly resulting in pre-existing neurocognitive alterations). For analyses that include patients with baseline GCS scores <14, we will analyze the subgroups of baseline GCS <14 vs. baseline GCS of 14 or 15. The significance level for all subgroup-based tests will be adjusted in order to keep the overall type I error rate less than 0.05. Results of subgroup analyses will be used primarily to confirm a consistent magnitude of treatment effect.

Power Analysis

The power of the primary analysis (frequency of abnormal GCS scores during DKA treatment) depends on the proportion of patients with GCS scores declining below 14 in each group. Previous data demonstrate that mental status abnormalities (GCS scores <14) occur in approximately 15% of children treated for DKA, and are associated with evidence of CE on neuroimaging.[8, 15] We assume that the treatment group with the highest rate of developing abnormal GCS scores would have an approximately 20% overall frequency of GCS scores below 14 and we desire to detect an absolute beneficial treatment effect of 7.5% with 90% power. Using a two-sided Type I error rate of 0.025 and the hypothesized proportions yields a required total sample size of approximately 1200 patients. Allowing for non-adherence to assigned treatment of up to 5% raises the required number to $1200/0.95^2$, or about 1330. In order to adjust for O'Brien-Fleming interim monitoring, a 2% increase will be made, bringing the sample size to approximately 1360. This represents the number of patients that present with GCS scores of at least 14. We estimate that approximately 10% of eligible patients will present with GCS scores less than 14. This means that in the period required to enroll 1360 patients presenting with normal GCS scores, about 150 with abnormal scores will be enrolled. Thus, the total planned enrollment is 1510.

Data and Safety Monitoring Board

This study will be monitored by a Data and Safety Monitoring Board (DSMB) approved by the funding agency (NICHD). The FLUID DSMB is composed of five doctorate-level members not affiliated with the study, including experts in the fields of emergency medicine, pediatric critical care, pediatric endocrinology, neuropsychology, and biostatistics. The DSMB will meet yearly and the monitoring plan for this study will include three interim analyses after approximately one-fourth, one-half, and three-fourths of the target sample size has been achieved. The DSMB will make recommendations regarding study conduct, data quality, participant safety, and continuing or stopping the trial.

Discussion

DKA-related cerebral injury is the major cause of mortality and morbidity in children with Type 1 diabetes.[34-36] DKA occurs frequently in children and is often present at the time of diagnosis of diabetes.[37] DKA may also occur in children with established diabetes during illness, diabetes equipment malfunction or diabetes mismanagement. Clinically-overt CE (CE) occurs in 0.5-1% of DKA episodes[5, 6] and has a high mortality rate (21-24%), Survivors frequently are left with permanent neurological deficits.[5, 6] Furthermore, children without overt neurological symptoms during DKA treatment may nonetheless have subtle evidence of brain injury after recovery from DKA, particularly memory deficits.[11] Some have postulated that excessive rates of fluid administration are responsible for DKA-related CE.[13, 38, 39] Recent investigations, however, suggest that dehydration and cerebral hypoperfusion may be associated with DKA-related cerebral injury.[6, 7, 16, 17] The association between fluid therapy and DKA-related cerebral injury has never been investigated in a randomized controlled trial. Therefore the current study is timely and necessary. The PECARN FLUID Study will test the associations of fluid therapy not only with acute neurological events during DKA treatment, but also with long-term neurocognitive outcomes.

Clinically-overt CE, resulting in marked neurological depression, is infrequent, however, more subtle CE occurs with much greater frequency and is present in most children with DKA.[8-10] Studies using CT or MR imaging in children with DKA and in animal models of DKA have shown that CE may be present before treatment as well as during therapy.[8-10, 40] Children with abnormal mental status during DKA treatment (assessed by GCS scores) are more likely to have subtle CE (measured as narrowing of the cerebral ventricles) than those with normal mental status throughout treatment.[8] Abnormal GCS scores during DKA treatment have also been associated with greater magnetic resonance diffusion-weighted imaging changes indicative of CE.[15] These data suggest that CE is not a rare phenomenon in children with DKA, but rather that CE occurs frequently with varying severity. Severe, clinically-overt CE that occurs in 0.5-1% of children with DKA likely represents only the most extreme presentation of a common phenomenon.

Data suggest that even subtle DKA-related CE may not be without long-term consequences. One important study demonstrated that children with diabetes who had experienced DKA performed more poorly in tests of memory capacity compared to children with diabetes who had never had DKA.[11] Most children in that study had experienced only one DKA episode, generally at the time of diagnosis of diabetes, and the DKA group was nearly identical to the non-DKA group in regard to duration of diabetes, measures of glycemic control and frequency of hypoglycemic episodes. Exposure to DKA has similarly been shown to decrease maze learning ability in a rodent diabetes model.[41] These data suggest that complications of DKA may extend beyond the acute period and may affect neurocognitive function and quality of life for substantial numbers of children with Type 1 diabetes.

Because children with DKA frequently present with normal or only modestly altered mental status but may subsequently experience a decline in mental status during treatment, investigators questioned whether some aspects of treatment might be responsible.[12, 13, 38, 39, 42-44] For decades it has been hypothesized that rapid fluid infusion with rapid changes in serum osmolality might lead to brain cell swelling. [12, 13, 38, 39] Although this hypothesis is intuitively simple and attractive, data to support this hypothesis have been lacking. Properly controlled retrospective studies have not detected associations between osmotic changes during treatment and risk of CE.[6, 45, 46] Furthermore, although neurological decline associated with CE often occurs during DKA treatment, several reports document the occurrence of symptomatic CE in children with DKA prior to the initiation of therapy. [6, 47, 48] These data suggest that CE may not be primarily caused by osmotic shifts induced by therapeutic interventions, but instead that factors intrinsic to DKA may cause brain injury and this injury could be worsened during treatment. We and other investigators have hypothesized that DKA-related CE may be caused by cerebral hypoperfusion during DKA and the subsequent effects of reperfusion.[6, 7, 46, 49, 50]

Several additional lines of evidence suggest that DKA-related CE may not be caused by osmotic fluctuations. One important descriptive study demonstrated that many children with clinically-diagnosed DKA-related “cerebral edema”[50] have no evidence of edema on cerebral imaging studies done at the time of neurological decompensation, despite a profound degree of neurological depression. Repeat imaging studies performed hours or days later demonstrated evidence of CE, along with hemorrhage or cerebral infarction in some cases. These data suggest that CE may possibly be a *consequence* of cerebral injury during DKA, rather than the *cause* of injury, similar to hypoxic/ischemic brain injuries where edema typically develops after initial injury, as a consequence of cellular energy failure and blood-brain barrier dysfunction.

Data from both animal and human studies of DKA support the hypothesis that cerebral hypoperfusion and reperfusion may be involved in DKA-related brain injury. Cerebral blood flow (CBF) is low during untreated DKA and rises to levels above normal during treatment with insulin and saline.[7, 17] Brain cell swelling (cytotoxic edema) is present during untreated DKA.[40] During treatment with insulin and saline, vasogenic edema develops as CBF rises.[7] Furthermore, brain levels of high-energy phosphates are low during untreated DKA and cerebral lactate levels are elevated, suggesting inadequate CBF. [16] Early in the course of treatment with insulin and saline, brain high-energy phosphate levels decline further. Brain ratios of n-acetylaspartate (NAA) to creatine, an indicator of neuronal health, are also low during untreated DKA and initially decline during DKA treatment.[16] These data suggest that DKA per se may have adverse effects on CBF and metabolism, but more importantly, these data also suggest that further brain injury may occur initially during treatment with insulin and saline. These data therefore underscore the importance of determining whether variations in DKA treatment, particularly fluid infusion protocols, might affect the likelihood or severity of brain injury.

Whether rates of fluid infusion during DKA treatment in children influence the risk of clinically-overt CE has been a topic of much controversy. Several investigators have attempted to evaluate the effects of differences in fluid treatment through retrospective studies.[6, 12, 14, 45, 51, 52] The results of these studies have been variable, and consistent associations between rates of fluid infusion and risk of CE have not been found. One retrospective observational study documented similar rates of CE before and after an institutional DKA protocol change from more rapid rehydration with 0.9% saline to slower rehydration with 0.45% saline. [53] All of these retrospective studies, however, are by definition hampered by the lack of randomization of treatments with inherent tendency

toward bias caused by physicians' treatment decisions related to patient appearance and severity of presentation.

In a large retrospective study by our group, children with DKA-related CE were compared to controls with uncomplicated DKA, using multivariable analyses to control for variables related to DKA severity. In this study, we did not detect an association between fluid infusion rates and risk of clinically-apparent CE.[6] Although the analysis controlled for DKA severity to the extent possible in a retrospective study, treatment decisions may nonetheless have been biased by unmeasured factors related to patient appearance and clinical presentation. In addition, the study lacked the statistical power to make definitive conclusions regarding the effect of fluid infusion rates or sodium content.

Some studies have demonstrated that failure of the measured serum sodium concentration to rise as the glucose concentration decreases during therapy is associated with CE.[6, 14, 54, 55] Based on these data, one study evaluated a DKA protocol designed to avoid a decrease in sodium concentration by administering fluids at slow rates and utilizing fluids with relatively high concentrations of sodium.[56] Using this protocol, the investigators found that the serum sodium concentration rose as the glucose concentration fell in 90% of DKA episodes. No deaths or apparent permanent neurological injuries occurred, however, 6 patients (2.6%) required administration of mannitol because of alterations in mental status, likely indicative of CE. In sum, all previous studies of fluid treatment protocols in pediatric DKA have been hampered by retrospective data collection and/or lack of appropriate control or comparison groups. It is therefore imperative that a prospective randomized study be conducted to answer this question.

Taking into account recent data from cerebral imaging studies in children with DKA and in animal models of DKA, the optimal fluid treatment protocol is not obvious. If cerebral hypoperfusion during DKA plays a role in DKA-related cerebral injury and edema formation, arguments in favor or against all of the treatment arms in the PECARN FLUID study could be made. Conservative (slower) fluid resuscitation might serve to prolong the state of cerebral hypoperfusion, resulting in increased risk of cerebral injury. Furthermore, intravascular volume may decline during therapy as intravascular osmolality decreases. If fluid resuscitation is inadequate during this time, cerebral hypoperfusion may be worsened. Use of low sodium content fluids could exacerbate this problem. Conversely, it could be argued that more conservative fluid therapy might help to decrease vasogenic CE later in the course of DKA treatment, particularly if breakdown of the blood-brain-barrier occurs.

At present, the impact of fluid resuscitation protocols on DKA-related brain injury in children remains unknown. The design of the PECARN FLUID Study will allow us to determine the effect not only of fluid infusion rate, but also the sodium content of fluids. This study will be the first prospective clinical trial to provide evidence for definitive recommendations in regard to fluid rehydration therapy in the setting of pediatric DKA.

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Appendix: Structure of PECARN and the research team and details of study data management

This study is being conducted through the Pediatric Emergency Care Applied Research Network (PECARN) [56, 57] and currently involves thirteen individual hospital sites. The research team is organized with careful attention to specification of roles and clear lines of responsibility.

The fluid study PI's coordinate and oversee all aspects of the study, along with the study Project Administrator and the Project Data Coordinator Center (DCC). The participating PECARN EDs are divided into 6 research nodes. Each node in PECARN supervises 3 PECARN EDs. Each study site has a research coordinator who is responsible for the overall study organization at that site, coordination of a patient enrollment plan at that site, day-to-day data collection at the respective site and transmission of data to the DCC, overseen by the study site PI.

At each of the participating PECARN centers, the physician site co-investigator ("Site PI," an emergency physician) is responsible for the overall conduct of the study at that site. These investigators work closely with their Divisions/Departments of Pediatric Endocrinology and Pediatric Critical Care Medicine. Once received at the DCC, study data will be managed by DCC data mangers and analyzed by DCC statisticians.

Research team committees

The study Steering Committee, consisting of the PIs, the 12 other Site PIs, the Project Manager and Data Manager, and the PI of the DCC, oversee the performance of the study, and resolve and adjudicate study problems as they arise. The Publication Committee, which includes the PIs, and all Site PIs, is responsible for reviewing and approving proposed study manuscripts, and approving authorship agreements. This committee works closely with the PECARN Grant Writing and Publication Subcommittee, which serves in a similar capacity for all of PECARN.

Project Manager and Data Manager

The Project Manager and Data Manager at the DCC work with the PIs on the coordination and oversight of this study. The Project Manager helps the PIs organize research study meetings and communications, arrange travel accommodations, maintain study documents in the virtual electronic website, and answer questions regarding budget and subcontracts. S/he assists the Data Manager based at the DCC. The Project Manager organizes and monitors inter- and intra-nodal research activities including institutional review board submissions, electronic transmission of data to the DCC, and report generation. The Project Manager also assists with the preparation of documentation such as study progress reports, and interacts closely with the Data Manager, both based at the DCC.

The primary responsibility of the Data Manager at the DCC, supervised by the PI of the DCC, is to oversee the timely transmission of high-quality data as well as its subsequent management. The Data Manager helps to design the electronic database along with other

DCC personnel. In cooperation with the study PIs and the Project Manager, the Data Manager coordinates and provides the instruction on the Manual of Operations and oversees multiple data entry quality assurance.

Study communications and training plan

The communications infrastructure of PECARN is well established. Before the initiation of data collection, the members of the study Steering Committee and all site research coordinators met for a two-day conference to receive instruction in the study Manual of Operations. At that time, research coordinators and site PIs also received small group instruction on the conduct of the neurocognitive testing by Dr. Ghetti and several graduate level assistants. Each research coordinator conducted a minimum of 4 observed practice sessions including all of the neurocognitive testing procedures. Each session was followed by feedback and additional practice. Equivalent training is provided when new sites and reseach coordinators join the study. The Steering Committee and all site PIs attend two PECARN meetings annually throughout the course of this study to discuss study issues and instruct site PIs. Each site PI instructs the group of ED physicians at their home institutions about the study, and serves as a local advocate for the study, and coordinates the collaboration and communications between members of the Divisions of Pediatric Emergency Medicine, Pediatric Critical Care and Pediatric Endocrinology. Throughout the study, the Steering Committee has monthly telephone conference calls, or more frequent conference calls as necessary.

Data management and transmission to the Data Coordinating Center (DCC)

Study data will be entered at each site onto a secure, encrypted, password-protected virtual private network (VPN) connecting to a secure, password-protected database at a computer server. Site research coordinators will perform double entry to insure accuracy. The online data entry screens will contain range and logic checks to minimize data entry errors. The Data Manager will monitor data accuracy, contact sites with repeated data entry errors, and identify ways to resolve these errors.

Study monitoring

All PECARN studies undergo site monitoring, coordinated by the DCC in conjunction with the study PIs. The site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Each site was visited by a PECARN monitor during the first year of the study. Additional in-person and/or remote monitoring visits are occurring annually.

In addition to the site monitoring visits, neurocognitive testing procedures are periodically re-evaluated to insure that each site continues to conduct these procedures according to standardized methods. Each research coordinator responsible for neurocognitive testing is videotaped conducting the tests and the video is reviewed by the collaborating neuropsychologist. Any deviations from the correct testing procedures are reviewed with the site research assistants and corrected.

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Table 1

Treatment Protocol Overview

	Protocol A1	Protocol A2	Protocol B1	Protocol B2
Standard initial fluid bolus *	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline
Additional intravenous fluid bolus	Additional 10 cc/ kg of 0.9% saline	Additional 10 cc/ kg of 0.9% saline	No additional bolus	No additional bolus
Assumed fluid deficit	10% of body weight	10% of body weight	5% of body weight	5% of body weight
Replacement of deficit	replace half of fluid deficit + maintenance fluids over initial 12 hours, remaining deficit + maintenance fluids over subsequent 24 hours	replace half of fluid deficit + maintenance fluids over initial 12 hours, remaining deficit + maintenance fluids over subsequent 24 hours	replace deficit + maintenance fluids evenly over 48 hours	replace deficit + maintenance fluids evenly over 48 hours
Fluid used for deficit replacement	0.45% saline	0.9% saline	0.45% saline	0.9% saline

* **NOTE:** This is standard treatment at all participating centers and is not part of the study protocol. Consent will occur during this initial fluid bolus after which the study treatment will be randomized.

Table 2

Summary of data collection during DKA

Data to be collected	Frequency of measurement
DEMOGRAPHIC AND HISTORICAL DATA	
• *Demographic data* (age, gender, race/ethnicity, parental income and education level) • *Diabetes history for children with known DM* (age at diagnosis of DM, HbA1c over past year, number of previous DKA episodes, number of previous episodes of severe hypoglycemia) • *Clinical data* (medical conditions other than diabetes, presence/severity of headache, assessment of peripheral perfusion)	• At time of enrollment
BIOCHEMICAL MONITORING	
• Blood glucose concentration	• At presentation and hourly
• Electrolytes (Na, K, Cl, HCO_3, BUN, Cr)	• At presentation and approximately every 2-4 hours (per usual site protocols)
• Venous pH and pCO2	• At presentation and approximately every 2-4 hours (per usual site protocols)
• Serum Ca, Phos, Mg	• At presentation and approximately every 4-8 hours (per usual site protocols)
ASSESSMENT OF NEUROLOGICAL FUNCTION	
• Mental status assessment (GCS scores)	• At enrollment and hourly
• Brief memory assessment (digit span recall)	• At enrollment and every 4 hours during normal waking hours

Table 3

Summary of neurocognitive testing 3 months after DKA recovery

AGE	TESTING PROCEDURES
• Younger than 3 years	• No neurocognitive evaluation
• 3-5 years	• IQ assessment – abbreviated WPSSI-R • Memory assessment – abbreviated versions of color task and spatial location task
• 6 -18 years	• IQ assessment – WASI • Memory assessment – color task and spatial location task