PCCL Session: Summary Report and Resources

PCCL session topic and date:

Sweet and Sour: Managing Severe Diabetic Ketoacidosis (DKA)

January 19, 2024.

Learning objectives:

- **Understand pathophysiology, assessment and treatment of cerebral edema in severe pediatric DKA.**
- **What is meant by "corrected" sodium measurement and is it essential?**
- **How and when to make the decision to switch to ½ Normal Saline.**
- **What is the most efficacious ventilation strategy if the patient begins to tire?**

Brief case presentation:

11-year-old Male (39kg) presented with 4 days of illness and altered level of consciousness at 0200h, unconscious at 0600h, brought to ED at that time.
No past medical history or medications, unknown immunization status.
Assessment and vital signs:

- GCS 6 (1-1-4, BP 80s/50s, HR 80, RR 40-50, T 30.4, Sats 94% RA, Kussmaul respirations, ketotic breath, PERL @4mm, grimace on abdominal palpation, capillary refill 5-6 seconds)

Investigations:
POC glucose >33.3mmol/L
POC UA – ketonuria
VBG: pH <6.80, pCO_2 10mmhg, HCO_3 2mmol/L, K^+ 2.7mmol/L

Key Concepts:

Cerebral Edema:

- **A patient with severe DKA and a decline in their Glasgow Coma Scale (GCS) should be treated for cerebral edema without the need for central nervous system (CNS) imaging**
- **Treatment of cerebral edema should include either 3%NaCl or Mannitol**

Sodium:

- **The goal in treatment of DKA is for slow correction of sodium changes, and requires repeated, regular checking of electrolytes, especially when any changes to fluid content is made**
- **All children with DKA are recommend to receive fluid administration, with most children with moderate to severe DKA requiring 20mls/kg fluid bolus to restore perfusion**
- **Serum sodium can be 'corrected' to allow for the effect of severe glycemia - this indicates the degree of hypertonicity due to osmotic diuresis. Most children with DKA have preserved renal**

function (at least initially) and their hypertonicity will almost always be due to hyperglycemia. In summary: in the acute (and provincial) management of severe DKA it is more important to avoid rapid falls in serum sodium - no need to "correct" the values.

Airway/Breathing

- **Intubation of a patient with potentially increased intracranial pressure (ICP) should have sufficiently deep sedation to mitigate a spike in ICP.**
- **The decision to intubate a patient with severe DKA vs support with non-invasive ventilation (NIV) is complex. Discussion with the PICU team regarding these decisions is suggested.**

Resources:

- DKA protocol used provincially: Diabetic Ketoacidosis Protocol (bcchildrens.ca)
- Kuppermann, N., Ghetti, S., Schunk, J. E., Stoner, M. J., Rewers, A., McManemy, J. K., ... & Glaser, N. S. (2018). Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *New England Journal of Medicine*, *378*(24), 2275-2287. PECARN NEJM 2018.
- Basnet, S., Venepalli, P. K., Andoh, J., Verhulst, S., & Koirala, J. (2014). Effect of normal saline and half normal saline on serum electrolytes during recovery phase of diabetic ketoacidosis. *Journal of intensive care medicine*, *29*(1), 38-42. Basnet et al JICM 2012.
- Badawi, N. E. S., Hafez, M., Eldin, H. S., Abdelatif, H. M., Atef, S., Ismail, M. M., & Arafa, N. (2021). Outcome of the use of 0.9% saline versus 0.45% saline for fluid rehydration in moderate and severe diabetic ketoacidosis in children. *Egyptian Pediatric Association Gazette*, *69*(1), 1-10. Badawi et al. Egyptian Pediatric Association Gazette 2021.
- Glaser, N., Fritsch, M., Priyambada, L., Rewers, A., Cherubini, V., Estrada, S., ... & Codner, E. (2022). ISPAD clinical practice consensus guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatric diabetes*, *23*(7), 835-856. ISPAD DKA and HHS 2021
- Sodium Guide from Dr. Sarah Riedlinger (pediatric endocrinologist)

ORIGINAL ARTICLE

Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis

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ABSTRACT

BACKGROUND

Diabetic ketoacidosis in children may cause brain injuries ranging from mild to severe. Whether intravenous fluids contribute to these injuries has been debated for decades.

METHODS

We conducted a 13-center, randomized, controlled trial that examined the effects of the rate of administration and the sodium chloride content of intravenous fluids on neurologic outcomes in children with diabetic ketoacidosis. Children were randomly assigned to one of four treatment groups in a 2-by-2 factorial design (0.9% or 0.45% sodium chloride content and rapid or slow rate of administration). The primary outcome was a decline in mental status (two consecutive Glasgow Coma Scale scores of <14, on a scale ranging from 3 to 15, with lower scores indicating worse mental status) during treatment for diabetic ketoacidosis. Secondary outcomes included clinically apparent brain injury during treatment for diabetic ketoacidosis, short-term memory during treatment for diabetic ketoacidosis, and memory and IQ 2 to 6 months after recovery from diabetic ketoacidosis.

RESULTS

A total of 1389 episodes of diabetic ketoacidosis were reported in 1255 children. The Glasgow Coma Scale score declined to less than 14 in 48 episodes (3.5%), and clinically apparent brain injury occurred in 12 episodes (0.9%). No significant differences among the treatment groups were observed with respect to the percentage of episodes in which the Glasgow Coma Scale score declined to below 14, the magnitude of decline in the Glasgow Coma Scale score, or the duration of time in which the Glasgow Coma Scale score was less than 14; with respect to the results of the tests of short-term memory; or with respect to the incidence of clinically apparent brain injury during treatment for diabetic ketoacidosis. Memory and IQ scores obtained after the children's recovery from diabetic ketoacidosis also did not differ significantly among the groups. Serious adverse events other than altered mental status were rare and occurred with similar frequency in all treatment groups.

CONCLUSIONS

Neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Health Resources and Services Administration; PECARN DKA FLUID ClinicalTrials.gov number, NCT00629707.)

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A Quick Take is available at NEJM.org

Clinically apparent brain injuries occur in 0.5 to 0.9% of episodes of diabetic ketoacidosis in children; these brain injuries manifest as sudden neurologic decline and are often associated with morbidity and mortality.[1-3] Among patients without obvious neurologic decline during treatment for diabetic ketoacidosis, subtle neurologic alterations are often present after recovery, including deficits in memory, attention, and IQ[4-7] and changes in cerebral microstructure.[4,8,9]

Early theories to explain diabetic ketoacidosis–related brain injury suggested that rapid administration of intravenous fluids reduces serum osmolality, which results in brain swelling.[10,11] Therefore, many treatment protocols for diabetic ketoacidosis in children advocate slow rehydration with isotonic fluids. Retrospective reviews have been used to support these strategies; however, those studies are subject to bias owing to the higher rates of brain injury that have been seen in children who are more dehydrated[2] and therefore receive larger volumes of fluid. In addition, such studies have often included patients who had been selectively referred because of the severity of their illness from facilities that were often not specifically pediatric centers and that used treatment protocols that differed from those at pediatric centers.[10,12,13] Rates of clinically apparent brain injury have remained stable over time,[2,14,15] and properly controlled retrospective studies have not shown associations between the fluid administration rate and brain injury.[2,3] Instead, data suggest that brain injury may result from abnormalities in cerebral perfusion and inflammation that occur during episodes of diabetic ketoacidosis.[2,16] In the current trial, we investigated the effects of specific intravenous fluid regimens on neurologic outcomes in children with diabetic ketoacidosis.

METHODS

OVERVIEW OF THE TRIAL

We conducted this randomized, controlled trial at 13 emergency departments in the Pediatric Emergency Care Applied Research Network (PECARN), all of which were located in urban centers in the United States. We used a 2-by-2 factorial design to compare four rehydration treatment regimens in children with diabetic ketoacidosis (Table 1).[17] We evaluated the effects of rehydration rate and fluid sodium chloride content on neurocognitive outcomes, including neurologic status during the episode of diabetic ketoacidosis and memory and IQ after recovery from diabetic ketoacidosis. Details of the trial methods were published previously[17] and are also provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL OVERSIGHT

The trial was designed by the first and last authors (principal investigators), with input from site investigators; collaborators from the PECARN data coordinating center; the PECARN quality, safety, and regulatory affairs subcommittee; the PECARN protocol review and development subcommittee; and the PECARN grant writing and publications subcommittee. Research coordinators collected the data under the supervision of the site investigators. The PECARN data coordinating center was responsible for data quality control and analyses. A data and safety monitoring board, which oversaw the conduct of the trial, included an expert in each of the following disciplines: emergency medicine, pediatric critical care, pediatric endocrinology, neuropsychology, and biostatistics. The data and safety monitoring board convened before enrollment, at the time of three scheduled interim efficacy analyses, and at the time of four additional scheduled reviews of safety, enrollment, and follow-up data. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. There was no industry funding for this trial, and there were no agreements concerning confidentiality of the data between the sponsor and the authors or institutions. All the authors reviewed drafts of the manuscript and agreed with the decision to submit the manuscript for publication.

PATIENTS

Children were eligible for enrollment in the trial if they were between 0 and 18 years of age and had received a diagnosis of diabetic ketoacidosis (defined as a blood glucose level of >300 mg per deciliter [16.7 mmol per liter] and either a venous pH of <7.25 or a serum bicarbonate level of <15 mmol per liter). Key exclusion criteria[17] were underlying disorders that could affect mental status testing or neurocognitive evaluation; concurrent alcohol or narcotics use, head trauma,

or other conditions that could affect neurologic function; diabetic ketoacidosis for which the patient had already received substantial treatment; known pregnancy; or factors for which treating physicians determined that a specific fluid and electrolyte therapy was necessary. Children who presented with a Glasgow Coma Scale score of 11 or lower (on a scale ranging from 3 to 15, with lower scores indicating worse mental status) were excluded after year 2 because many participating clinicians believed that fluid regimens for such children should not be determined on the basis of randomization.

TREATMENTS

Written informed consent was obtained from the parents or guardians of all enrolled patients. Assent was obtained from patients whose age met the minimum age for assent according to their local institutional review board. Children were then randomly assigned to one of four treatment regimens: fast rate of rehydration with fluid that had 0.45% sodium chloride content, fast rate of rehydration with fluid that had 0.9% sodium chloride content, slow rate of rehydration with fluid that had 0.45% sodium chloride content, and slow rate of rehydration with fluid that had 0.9% sodium chloride content. Details of the treatment regimens are provided in Table 1. Randomization was stratified according to baseline Glasgow Coma Scale score (14 or 15 vs. <14) and center (if the Glasgow Coma Scale score was <14).[17] To avoid excessive restriction of the population available for enrollment, patients who had previously undergone randomization and subsequently had another episode of diabetic ketoacidosis during the trial were eligible to undergo randomization a second time. A patient could undergo randomization no more than twice. Additional details are provided in the Statistical Analysis section and in the protocol.

Treatment for diabetic ketoacidosis other than the rate of administration and the sodium chloride content of the fluid was identical in the four treatment groups.[17] After administration of intravenous fluid boluses, insulin treatment was initiated as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. To prevent hypoglycemia during insulin treatment, dextrose was added to the study fluids when the serum glucose level declined below 200 to 300 mg per deciliter (11.1 to 16.7 mmol

Table 1. Treatment Regimens.

Variable	Fast Administration of 0.45% Sodium Chloride Solution	Fast Administration of 0.9% Sodium Chloride Solution	Slow Administration of 0.45% Sodium Chloride Solution	Slow Administration of 0.9% Sodium Chloride Solution
Standard initial fluid bolus*	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution	10 ml per kilogram bolus of 0.9% sodium chloride solution
Additional intravenous fluid bolus	10 ml per kilogram of 0.9% sodium chloride solution	10 ml per kilogram of 0.9% sodium chloride solution	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
Process for replacement of deficit	During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.	During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.	Replace deficit, plus maintenance fluids, evenly during a period of 48 hours.	Replace deficit, plus maintenance fluids, evenly during a period of 48 hours.
Fluid used for replacement of deficit†	0.45% sodium chloride solution	0.9% sodium chloride solution	0.45% sodium chloride solution	0.9% sodium chloride solution

* Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter).

† Replacement of potassium was provided with the use of an equal mixture of potassium chloride and potassium phosphate or an equal mixture of potassium acetate and potassium phosphate. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites.

per liter). Patients and their parents or guardians were unaware of the treatment-group assignments. It was not possible for clinicians to be unaware of the treatment-group assignments because of the need to know the fluid protocol for clinical decision making.

OUTCOMES

The primary trial outcome was deterioration of neurologic status (as evidenced by two consecutive Glasgow Coma Scale scores of <14 during any hour within the first 24 hours of treatment for diabetic ketoacidosis). Secondary outcomes included short-term memory during treatment for diabetic ketoacidosis (forward and backward digit-span recall; scores range from 0 to 16, with higher scores indicating better short-term memory)[18]; clinically apparent brain injury (defined as a deterioration in neurologic status leading to initiation of hyperosmolar therapy or endotracheal intubation or resulting in death) during treatment for diabetic ketoacidosis; and short-term memory, contextual memory, and IQ 2 to 6 months after the episode of diabetic ketoacidosis. In the digit span test, participants are asked to repeat a sequence of numbers presented orally. In the "forward" task, participants are asked to repeat numbers in order, as presented. In the "backward" task, participants are asked to list the numbers in reverse order. The test stops when participants report the incorrect sequence twice for a given digit-span length.

To address variations in the diagnosis of clinically apparent brain injury, records of encounters with patients in which hyperosmolar therapy, endotracheal intubation, or death were documented were reviewed by an adjudication committee that included two pediatric critical care physicians and one pediatric emergency medicine physician, all of whom were unaware of the treatment-group assignments. Committee members confirmed or rejected each diagnosis of clinically apparent brain injury on the basis of published criteria.[19]

ASSESSMENTS

Assessments of Mental Status

Glasgow Coma Scale scores were assessed at enrollment and hourly thereafter. Glasgow Coma Scale scores of less than 14 were confirmed by repeating the test 15 minutes later. For children 3 years of age or older, digit-span tests were conducted at enrollment and every 4 hours thereafter during normal waking hours. Glasgow Coma Scale and digit-span assessments continued for 24 hours or until resolution of diabetic ketoacidosis (as defined by the transition to subcutaneous insulin) if diabetic ketoacidosis resolved before the 24-hour time point.

Assessments of Memory Function and IQ

Patients 3 to 18 years of age were asked to return 2 to 4 months after discharge from the hospital for neurocognitive assessment but were allowed to return up to 6 months after discharge. Neurocognitive testing was rescheduled in the event of either hypoglycemia (defined as a glucose level of <70 mg per deciliter [3.9 mmol per liter]) or ketosis (defined as the presence of moderate or large urine ketones).

IQ was evaluated with the use of the Wechsler Abbreviated Scale of Intelligence[20] (in patients 6 years of age or older) and the Wechsler Preschool and Primary Scale of Intelligence short form (in patients 3 to 5 years of age).[21] At the same testing session, the digit-span test was repeated, and contextual memory was assessed with color and spatial-position tasks,[17] which evaluated item recognition and recollection of contextual detail. Shorter and simpler versions of these tasks were used for children 3 to 5 years of age.[17] Research personnel who conducted the cognitive testing and recorded outcome data were unaware of the treatment-group assignments, as were the trial investigators who oversaw this process.

STATISTICAL ANALYSIS

The primary analyses were performed according to the intention-to-treat principle. We also performed secondary analyses in the per-protocol population (which included patients who underwent randomization and received trial fluids per the protocol) and in the safety population (which included all patients who received any trial fluid) (details are provided in the protocol). Patients who had Glasgow Coma Scale scores of 14 or 15 at baseline were included in the primary analyses. Because patients who had Glasgow Coma Scale scores of less than 14 at baseline had already met the criterion for the primary outcome before enrollment, such patients were not included in the primary analyses but were included in the secondary analyses. Distinct encounters

with the same patient were considered to be independent events. Given that patients who underwent randomization a second time could have been randomly assigned to a treatment regimen that was different from the first regimen they had been assigned to, a single patient could be represented in more than one treatment group in the analyses. Cochran–Mantel–Haenszel tests were used to test the effects of the rate of administration and of the sodium chloride content of the fluid. Each of these factors was tested with the use of P values that were adjusted for multiplicity at a two-sided alpha level of 0.025.

We analyzed the magnitude of the decline in the Glasgow Coma Scale score and the duration of time in which the Glasgow Coma Scale score was less than 14 using Van Elteren tests, with adjustment for stratification variables. The incidence of clinically apparent brain injury was evaluated with the use of a Cochran–Mantel–Haenszel test. We tested for treatment interactions using regression models. To evaluate digit-span scores, we used a linear mixed-effects model to estimate time-dependent effects of the rate of administration and the sodium chloride content of the fluid. We assigned a digit-span score of zero in cases in which a patient had a Glasgow Coma Scale score of less than 14 to account for digit-span scores that could not be measured owing to mental status alterations. A random intercept and slope term for patient encounters and similar fixed terms for trial centers were included in the model.

The main analysis of memory function was based on the average of the children's correct recall rates of items in association with their color background or spatial location. Scores were excluded from the analysis if chance recognition of previously viewed items was observed (sensitivity index of <0.50; 5% of tests). Memory scores and IQ were compared with the use of a Van Elteren test, with adjustment for stratification variables. In cases in which a patient had more than one valid follow-up measurement, only the first measurement was included in the analysis. Significance levels for digit-span score and memory function were adjusted for multiple comparisons with the use of the Holm procedure.

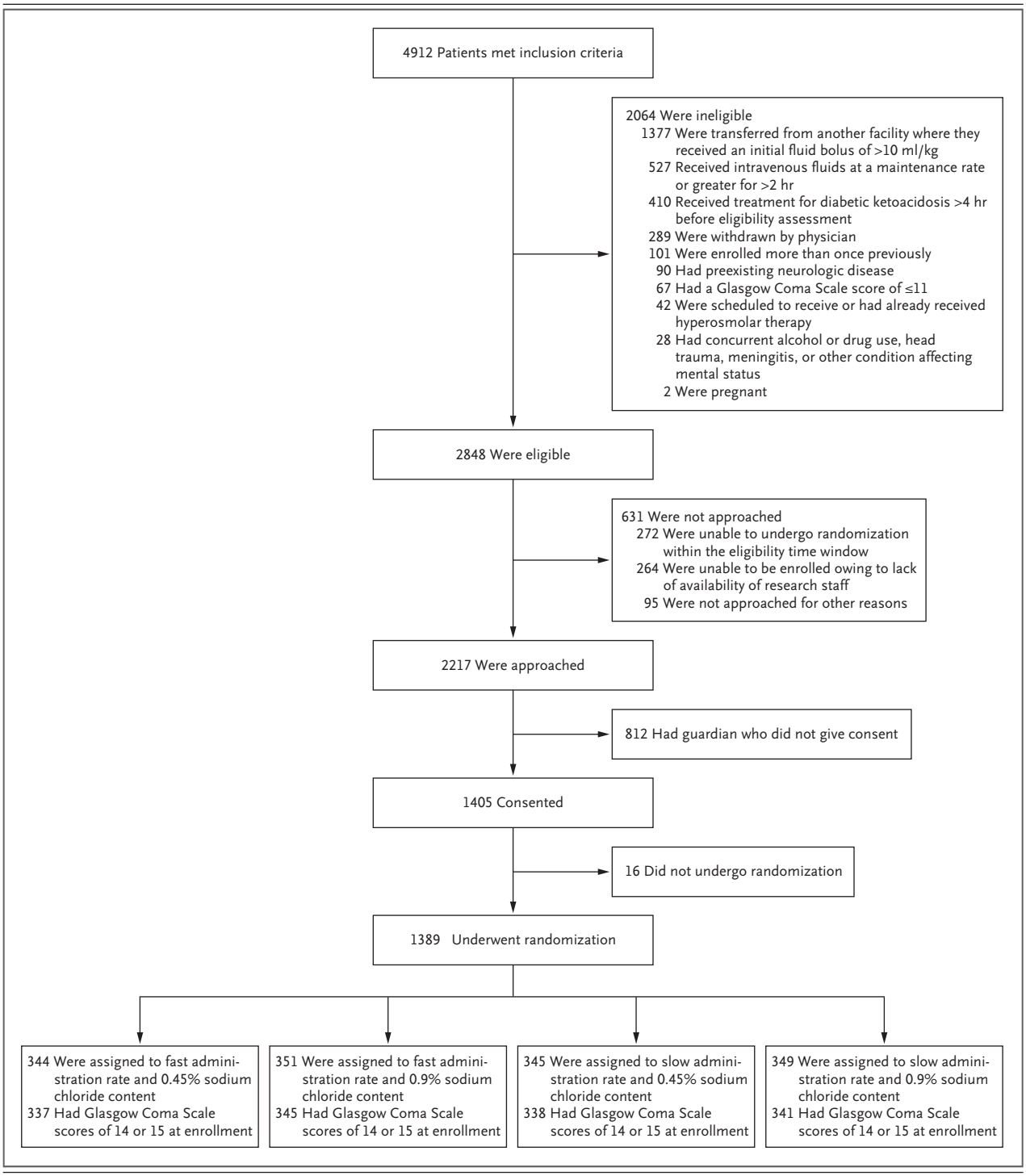
We also analyzed treatment effects in prespecified subgroups defined according to age (<6 years vs. ≥6 years), Glasgow Coma Scale score at baseline, and history of diabetic ketoacidosis (yes vs. no) using regression models, with adjustment for stratification variables. The overall type I error rate for the subgroup analyses was preserved at 0.05. Using the same methods, we explored treatment effects in eight subgroups defined according to various baseline characteristics that are associated with more severe diabetic ketoacidosis; results from four of these subgroups are reported and should be interpreted with caution owing to multiple comparisons. The analyses of statistical power and sample size have been described previously.[17] Our target sample size was 1360 patient encounters involving children who had baseline Glasgow Coma Scale scores of 14 or 15 (i.e., 1360 episodes of diabetic ketoacidosis that could be included in the primary analysis).

Two-sided O'Brien–Fleming stopping boundaries at the time of each interim efficacy analysis were calculated with the use of the alpha-spending function approach. The thresholds for significance at the first, second, and third interim analyses were 0.000006, 0.0008, and 0.0075, respectively. No safety concerns were identified, and the trial proceeded to completion.

RESULTS

PATIENTS

From February 2011 through September 2016, a total of 1255 children were randomly assigned to one of the four treatment regimens (Table 1). Among these 1255 patients, 132 had a second episode of diabetic ketoacidosis and underwent randomization a second time during the trial. Two additional patients who had a third episode of diabetic ketoacidosis inadvertently underwent randomization a third time. Therefore, a total of 1389 distinct episodes of diabetic ketoacidosis were evaluated. Patient enrollment and randomization status are shown in Figure 1. Demographic and clinical characteristics of the children, including status with respect to history of diabetes, did not differ significantly among the four groups (Table 2). Adherence to the assigned treatment regimens was excellent (Figs. S1 and S2 in the Supplementary Appendix, available at NEJM.org). Enrollment varied among the emergency departments; the number of patient encounters ranged from 23 to 239 (Table S1 in the Supplementary Appendix).



MENTAL STATUS DURING TREATMENT FOR DIABETIC KETOACIDOSIS

In 1361 episodes of diabetic ketoacidosis (98.0%), children presented with Glasgow Coma Scale scores of 14 or 15, and these episodes were therefore included in the primary analysis. During the course of the trial, the Glasgow Coma Scale score declined to below 14 in 48 (3.5%) of these episodes (Table 3). A total of 22 episodes (1.6%) resulted in the children receiving hyper-

Figure 1 (facing page). Enrollment and Randomization.
A total of 586 patients met multiple ineligibility criteria. Three patients who had a Glasgow Coma Scale score of 11 or lower were enrolled before the implementation of this exclusion criterion. Patients were permitted to undergo randomization a second time if they had a second episode of diabetic ketoacidosis during the trial, with each randomization considered to be a distinct encounter; hence, some children are represented more than once in this figure. A total of 1255 patients underwent randomization initially. Among these 1255 patients, 132 had a second episode of diabetic ketoacidosis and underwent randomization a second time during the trial. Two additional patients who had a third episode of diabetic ketoacidosis inadvertently underwent randomization a third time. Therefore, a total of 1389 distinct episodes of diabetic ketoacidosis were evaluated, as shown here. Enrollment sites were located in Boston, MA, Chicago, IL, Columbus, OH, Denver, CO, Houston, TX, New York, NY, Philadelphia, PA, Providence, RI, Sacramento, CA, Salt Lake City, UT, St. Louis, MO, Washington, DC, and Wilmington, DE.

osmolar therapy for possible cerebral edema or brain injury. In 12 episodes (0.9%), the children had clinically apparent brain injury (confirmed by adjudication) — a rate that was similar to previously documented frequencies.[1-3] Most of the 12 patients presented with severe acidosis and hypocapnia (Table S2 in the Supplementary Appendix). One of the 12 patients died, and the remaining patients recovered without overt neurologic deficits.

There were no significant differences among the groups in the percentage of episodes in which the Glasgow Coma Scale score declined to below 14, in the magnitude of decline in the Glasgow Coma Scale score, or in the duration of time in which the Glasgow Coma Scale score was less than 14 (Table 3, and Table S3 in the Supplementary Appendix). The Breslow–Day test for homogeneity of the odds ratios did not provide evidence against homogeneity ($P=0.39$ for administration rate; $P=0.67$ for sodium chloride content). The incidence of clinically apparent brain injury was higher in the slow rehydration groups than in the fast rehydration groups; however, the differences were not significant. Digit-span scores during the episode of diabetic ketoacidosis did not differ significantly among the four groups, although point estimates for the rate of improvement in forward digit-span scores favored more rapid rehydration ($P=0.06$).

SUBGROUP ANALYSES OF MENTAL STATUS

Analyses of the relative risk of a decline to below 14 in the Glasgow Coma Scale score in subgroups defined according to age and history of diabetic ketoacidosis among patients who had Glasgow Coma Scale scores of 14 or 15 at baseline did not show differential treatment effects (Fig. S3 in the Supplementary Appendix). In the subgroups of patients who had more severe diabetic ketoacidosis (a pH or partial pressure of carbon dioxide [Pco_2] level in the lowest quartile or a blood urea nitrogen level or glucose level in the highest quartile), the percentage of episodes in which the Glasgow Coma Scale score declined to below 14 and the percentage of episodes in which clinically apparent brain injury was confirmed did not differ significantly among the groups (Table S4 in the Supplementary Appendix). The effect of rehydration rate on forward digit-span scores differed in the subgroup defined according to Pco_2 level ($P=0.03$ for the interaction between treatment and Pco_2 level), with faster improvement in the rapid rehydration groups than in the slow rehydration groups among patients with a low Pco_2 level ($P=0.03$). The effect of rehydration rate on backward digit-span scores differed in the subgroup defined according to pH level ($P=0.01$ for the interaction between treatment and pH level), with faster improvement in the rapid rehydration groups than in the slow rehydration groups among patients with a low pH ($P=0.01$).

NEUROCOGNITIVE ASSESSMENTS AFTER RECOVERY FROM DIABETIC KETOACIDOSIS

In all, 1287 episodes occurred in children older than 3 years of age who met the criteria for follow-up neurocognitive testing. The children involved in 387 of these episodes (30.1%) were either lost to follow-up or declined to return for neurocognitive testing (see "Power and Sample Size" in the Supplementary Appendix for sensitivity analyses regarding missing data). Data were analyzed for 855 episodes (66.4%), for which follow-up occurred within 6 months after the patient's discharge from the hospital (756 within 4 months and 99 between 5 and 6 months). There were no significant differences in neurocognitive outcomes after recovery among the trial groups (Table S5 in the Supplementary Appendix).

RESULTS AMONG PATIENTS TREATED ACCORDING TO THE PROTOCOL

Fluid hydration regimens that were administered in 115 episodes (8.3%), including 107 (7.9%) analyzed for the primary outcome, deviated sufficiently from the assigned treatment regimen that the rate of administration or sodium chloride content of the fluid was more similar to other treatment regimens than to the assigned regimen. We excluded these episodes and repeated the analyses to determine whether these protocol deviations influenced the outcomes (Tables S6 and S7 in the Supplementary Appendix). The results of these analyses showed no significant differences among the groups.

RESULTS AMONG PATIENTS ACCORDING TO TREATMENT RECEIVED

We modeled continuous versions of fluid administration rate and sodium chloride content in

Table 2. Demographic and Clinical Characteristics of the Trial Population.*

Variable	Fast Administration of 0.45% Sodium Chloride Solution (N=344)	Fast Administration of 0.9% Sodium Chloride Solution (N=351)	Slow Administration of 0.45% Sodium Chloride Solution (N=345)	Slow Administration of 0.9% Sodium Chloride Solution (N=349)
Demographic characteristics				
Age — yr	11.5±4.06	11.8±4.26	11.6±4.09	11.6±3.89
Age <6 yr — no. (%)	43 (12.5)	42 (12.0)	42 (12.2)	35 (10.0)
Race — no./total no. (%)†				
White	235/327 (71.9)	232/328 (70.7)	247/331 (74.6)	243/329 (73.9)
Black	73/327 (22.3)	82/328 (25.0)	68/331 (20.5)	63/329 (19.1)
Other	19/327 (5.8)	14/328 (4.3)	16/331 (4.8)	23/329 (7.0)
Hispanic ethnic group — no./total no. (%)†	48/331 (14.5)	62/335 (18.5)	49/329 (14.9)	69/342 (20.2)
Male sex — no. (%)	165 (48.0)	164 (46.7)	158 (45.8)	163 (46.7)
Diabetes history				
Previous diagnosis of diabetes — no. (%)	174 (50.6)	182 (51.9)	185 (53.6)	192 (55.0)
Duration of diabetes — yr	4.8±3.1	5.1±3.2	4.9±3.4	4.8±3.3
History of severe hypoglycemia — no./total no. (%)				
None	135/170 (79.4)	139/178 (78.1)	144/183 (78.7)	154/188 (81.9)
1 or 2 episodes	20/170 (11.8)	26/178 (14.6)	29/183 (15.8)	25/188 (13.3)
>2 episodes	15/170 (8.8)	13/178 (7.3)	10/183 (5.5)	9/188 (4.8)
Previous episodes of diabetic ketoacidosis among patients with known diabetes — no./total no. (%)				
None	42/173 (24.3)	34/181 (18.8)	60/182 (33.0)	58/189 (30.7)
1 or 2	74/173 (42.8)	83/181 (45.9)	67/182 (36.8)	77/189 (40.7)
>2	57/173 (32.9)	64/181 (35.4)	55/182 (30.2)	54/189 (28.6)
Glycated hemoglobin level in previous yr — %‡	10.6±2.0	10.8±1.8	10.7±1.9	10.5±2.0
Mental status at randomization				
Glasgow Coma Scale score at randomization — no. (%)§				
<14	7 (2.0)	6 (1.7)	7 (2.0)	8 (2.3)
14	23 (6.7)	25 (7.1)	26 (7.5)	25 (7.2)
15	314 (91.3)	320 (91.2)	312 (90.4)	316 (90.5)
Forward digit-span recall¶	7.13±2.39	7.12±2.28	7.25±2.07	7.46±2.37
Backward digit-span recall¶	5.54±2.31	5.47±2.25	5.51±2.30	5.76±2.31

Table 2. (Continued.)

Variable	Fast Administration of 0.45% Sodium Chloride Solution (N=344)	Fast Administration of 0.9% Sodium Chloride Solution (N=351)	Slow Administration of 0.45% Sodium Chloride Solution (N=345)	Slow Administration of 0.9% Sodium Chloride Solution (N=349)
Laboratory values at presentation				
Glucose — mg/dl	519±153	524±150	523±170	522±156
Blood urea nitrogen — mg/dl	17±8	17±7	17±9	17±7
pH	7.17±0.09	7.16±0.10	7.16±0.10	7.16±0.11
Sodium — mmol/liter	134±5	134±5	134±5	134±5
Bicarbonate — mmol/liter	9±3	9±3	9±3	9±3
Pco_2 — mm Hg	26±7	26±7	26±8	27±7

* Plus–minus values are means ±SD. There were no significant differences ($P<0.05$) between the groups in any of the comparisons according to Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables. Patients were permitted to undergo randomization a second time if they had a second episode of diabetic ketoacidosis during the trial, with each randomization considered to be a distinct encounter; therefore, a patient could be represented in more than one group. A total of 132 patients had a second episode of diabetic ketoacidosis and underwent randomization a second time during the trial. Two additional patients who had a third episode of diabetic ketoacidosis inadvertently underwent randomization a third time. Therefore, a total of 1389 distinct episodes of diabetic ketoacidosis were evaluated Data shown are based on encounters. Percentages may not sum to 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

† Race and ethnic group were determined by either patient report or review of medical records.

‡ Data were available for 173, 173, 177, and 184 patients in the four listed groups, respectively.

§ Scores range from 3 to 15, with lower scores indicating worse mental status.

¶ Scores range from 0 to 16, with higher scores indicating better short-term memory. In the digit span test, participants are asked to repeat a sequence of numbers presented orally. In the "forward" task, participants are asked to repeat numbers in order, as presented. In the "backward" task, participants are asked to list the numbers in reverse order. The test stops when participants report the incorrect sequence twice for a given digit-span length.

regression analyses. To account for influences of clinical presentation on decisions of the clinicians to deviate from assigned treatment regimens, we included covariates that reflected the severity of diabetic ketoacidosis (levels of pH, Pco_2, glucose, sodium, and blood urea nitrogen), age, and whether the diabetes was new-onset or preexisting. Again, no significant effects of either fluid administration rate or sodium chloride content on acute neurologic outcomes were found (data not shown).

NONNEUROLOGIC ADVERSE EVENTS

Hyperchloremic acidosis was more common among patients who received fluid that had a 0.9% sodium chloride content than among those who received fluid that had a 0.45% sodium chloride content and more common among patients who received fluid at a rapid rate than among those who received fluid at a slow rate (Table S8 in the Supplementary Appendix). The 0.9% sodium chloride regimens were also associated with a higher incidence of hypocalcemia and hypophosphatemia than were the 0.45% sodium chloride regimens. A rapid rate of fluid administration was associated with a higher incidence of hypocalcemia but not a higher incidence of hypophosphatemia. Hypoglycemia and hypokalemia occurred at similar rates in the four groups. Serious adverse events occurred in less than 3% of participants (Table 4, and Table S9 in the Supplementary Appendix). The time to resolution of diabetic ketoacidosis and the duration of hospitalization were similar among the groups (Table S10 in the Supplementary Appendix).

DISCUSSION

In this randomized, controlled trial, with a 2-by-2 factorial design, that involved children with diabetic ketoacidosis, there were no significant differences in the rate of decline in mental status or in the rate of clinically apparent brain injury during treatment for diabetic ketoacidosis or in neurocognitive function after recovery from diabetic ketoacidosis among patients who received rehydration fluid at two different administration rates and with two different sodium chloride contents. The lowest rates of mental status decline and clinically apparent brain injury were in

Table 3. Mental Status Changes during Treatment for Diabetic Ketoacidosis.*

Outcome	Fast Administration of 0.45% Sodium Chloride Solution	Fast Administration of 0.9% Sodium Chloride Solution	Slow Administration of 0.45% Sodium Chloride Solution	Slow Administration of 0.9% Sodium Chloride Solution	Fast vs. Slow Administration		0.45% vs. 0.9% Sodium Chloride Solution		P Value for Interaction
					Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	
Primary outcome									
No. of episodes†	337	345	338	341					
Confirmed decline in Glasgow Coma Scale score to <14 — no. (%)‡	10 (3.0)	11 (3.2)	11 (3.3)	16 (4.7)	0.76 (0.44–1.33)	0.34	0.80 (0.46–1.40)	0.43	0.76
Secondary outcomes†									
No. of episodes	344	351	345	349					
Clinically apparent brain injury — no. (%)‡§	2 (0.6)	2 (0.6)	5 (1.4)	3 (0.9)	0.49 (0.15–1.64)	0.24	1.43 (0.46–4.40)	0.53	1.00
Digit-span recall test, forward slope¶	0.065±0.010	0.058±0.010	0.046±0.010	0.039±0.010		0.06		0.49	
Digit-span recall test, backward slope¶	0.052±0.009	0.053±0.009	0.042±0.009	0.043±0.009		0.29		0.91	

* Plus–minus values are means ±SE. Owing to the factorial nature of the trial, each patient is included in the comparisons of both administration rate and sodium chloride content.
† The data from 28 patients who had a baseline Glasgow Coma Scale score of less than 14 were excluded from the primary analysis and included in the secondary analyses.
‡ The results of this analysis were compared with the use of a Cochran–Mantel–Haenszel test stratified according to sodium chloride content (comparisons of fast vs. slow administration rate), administration rate (comparisons of 0.45% vs. 0.9% sodium chloride content), and trial site.
§ These patients received mannitol, hypertonic saline, or endotracheal intubation after randomization, and an adjudication committee deemed each patient to have had clinically apparent brain injury.
¶ Digit-span outcomes (scores ranging from 0 to 16, with higher scores indicating better short-term memory) over time were compared with the use of a mixed linear regression model with random patient-level intercept and slope terms and included fixed effects for trial site, time, and fluid administration rate and sodium chloride content. In cases in which a patient had a Glasgow Coma Scale score of less than 14, a digit span of zero was included in the accompanying 4-hour time interval. The digit-span results reported in this table refer to the slope parameter of the statistical model.

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Table 4. Adverse Events.*

Variable	Fast Administration of 0.45% Sodium Chloride Solution	Fast Administration of 0.9% Sodium Chloride Solution	Slow Administration of 0.45% Sodium Chloride Solution	Slow Administration of 0.9% Sodium Chloride Solution
Any adverse event — no. of episodes	114	124	118	129
Serious adverse event — no. (%)	5 (4.4)	4 (3.2)	11 (9.3)	10 (7.8)
Outcome — no. (%)				
Recovery, with return to baseline status	102 (89.5)	109 (87.9)	108 (91.5)	118 (91.5)
Recovery with sequelae	1 (0.9)	1 (0.8)	1 (0.8)	1 (0.8)
Persistence of symptoms	10 (8.8)	14 (11.3)	9 (7.6)	10 (7.8)
Death	1 (0.9)	0	0	0
Severity — no. (%)				
Mild	95 (83.3)	96 (77.4)	89 (75.4)	98 (76.0)
Moderate	12 (10.5)	25 (20.2)	22 (18.6)	30 (23.3)
Severe	7 (6.1)	3 (2.4)	7 (5.9)	1 (0.8)
Expected event — no. (%)	58 (50.9)	56 (45.2)	64 (54.2)	68 (52.7)
Common clinical adverse events — no. (%)†				
Headache	29 (25.4)	16 (12.9)	23 (19.5)	28 (21.7)
Oropharyngeal pain	9 (7.9)	11 (8.9)	10 (8.5)	9 (7.0)
Pyrexia	8 (7.0)	11 (8.9)	8 (6.8)	10 (7.8)
Abdominal pain	2 (1.8)	11 (8.9)	7 (5.9)	3 (2.3)
Constipation	3 (2.6)	4 (3.2)	2 (1.7)	11 (8.5)

* These data were analyzed in the safety population (all patients who underwent randomization and received any trial fluid). Because patients were permitted to undergo randomization twice, a patient could be represented in more than one group. Data are based on patient encounters (i.e., episodes of diabetic ketoacidoses) rather than on individual patients. An episode in which multiple adverse events of the same type occurred is counted once. An episode in which multiple adverse events of different types occurred is counted once for each type of adverse event. In cases in which multiple adverse events occurred in an episode, the most serious adverse event was used to describe seriousness, outcome, and severity.

† Common clinical adverse events were events that were reported in six or more patients in any group, excluding adverse events that were counted either as trial outcomes (mental status changes or brain injuries) or as expected nonneurologic adverse events (e.g., hypoglycemia or electrolyte abnormalities) (Table S8 in the Supplementary Appendix).

the rapid-rehydration groups, although the differences from other groups were not significant. Furthermore, analyses of the subgroups of patients who had more severe diabetic ketoacidosis suggested faster improvement in digit-span recall in the rapid fluid-administration groups than in the slow fluid-administration groups. These findings underscore the lack of a causal association between rapid fluid administration and diabetic ketoacidosis–related brain injury.

Clinically apparent diabetic ketoacidosis–related brain injury occurs infrequently but is an important cause of neurologic damage and death among children with diabetes.[1-3,22-24] Subtle brain injury often occurs during treatment for diabetic ketoacidosis in children and may contribute to cognitive decline.[4-9] Excessive fluid administration, which may result in rapid osmotic changes, has been widely suspected to cause brain injury,[11,25,26] but a more recent hypothesis suggests that cerebral hypoperfusion and the effects of reperfusion, along with neuroinflammation, are central to diabetic ketoacidosis–related brain injury.[2,27-29] The latter hypothesis is consistent with reports that document symptomatic and even fatal brain injury occurring before the initiation of treatment for diabetic ketoacidosis.[2,30] Furthermore, although cerebral edema is a feature of clinically apparent brain injury, edema often develops hours or days after a diagnosis of

brain injury,[19] a finding that suggests that edema may be a consequence, rather than the cause, of brain injury.

Studies involving children with diabetic ketoacidosis and studies in rodent models suggest similarities between diabetic ketoacidosis–related brain injury and ischemia–reperfusion injury. These include low cerebral blood flow and brain-cell swelling, along with low levels of high-energy phosphates in the brain and elevated lactate levels, during untreated episodes of diabetic ketoacidosis and cerebral hyperemia and vasogenic edema during treatment for diabetic ketoacidosis.[27-29,31-33] Although alterations in cerebral blood flow may be involved in diabetic ketoacidosis–related brain injury, the severity of cerebral hypoperfusion is unlikely to be sufficient to cause brain injury in the absence of other contributing factors. Diabetic ketoacidosis is associated with marked systemic increases in inflammatory cytokines and chemokines that may contribute to brain injury by activating cerebrovascular endothelia and increasing leukocyte adhesion.[16,34-36] Elevated levels of matrix metalloproteinase may promote blood–brain barrier dysfunction.[37]

The current trial has several limitations. First, the fluid administration rates were selected to represent upper and lower boundaries of current protocols used to treat pediatric diabetic ketoacidosis. It is possible that the use of administration rates outside this range may have resulted in different outcomes. However, given that the lowest rate of decline in mental status occurred in the group that received rapid rehydration with 0.45% sodium chloride solution, it seems unlikely that larger differences between protocols would have instead favored slower rehydration. Second, clinically apparent brain injury occurs in less than 1% of episodes, making it impractical to design a trial with sufficient statistical power to detect differences in this outcome. We used alterations in mental status as an indicator of subtle brain injury because children who have abnormal Glasgow Coma Scale scores during treatment for diabetic ketoacidosis are more likely to have subtle cerebral edema (on magnetic resonance imaging) than those who have normal mental status during treatment.[31,38] Nonetheless, it is possible that declines in Glasgow Coma Scale scores that occur during treatment for diabetic ketoacidosis reflect physiological processes that are different from those responsible for clinically apparent brain injury. Third, statistical power may have been reduced by the inclusion of repeat episodes, although such a reduction would be small.

In conclusion, in this prospective, randomized trial, neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes of diabetic ketoacidosis in children.

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Effect of Normal Saline and Half Normal Saline on Serum Electrolytes During Recovery Phase of Diabetic Ketoacidosis

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Abstract

Objective: This study aims to describe the effect of 0.9% saline (NS) versus 0.45% saline (half NS) when used during recovery phase of diabetic ketoacidosis (DKA) in children. Methods: A retrospective analysis of all children (1-18 years old) with DKA admitted in the pediatric intensive care unit (PICU) from 2005 to 2009 was undertaken. The primary end point was effect on serum electrolytes and acidosis. Results: Compared to 47 patients who received only NS (group A) throughout the recovery period and 33 patients who received NS but were switched to half NS (group B) at some point during recovery, 41 who received only half NS (group C) had a significant decrease in corrected serum sodium ($P < .01$). Hyperchloremia leading to nonanion gap acidosis was significantly greater in NS groups A and B than in half NS group C ($P < .01$). This led to increased duration of insulin infusion and length of stay in the PICU in the NS groups. Conclusions: Hyperchloremia resulting in nonanion gap acidosis can occur and may prolong the duration of insulin infusion and length of PICU stay in patients receiving NS as post-bolus rehydration fluid. Alternatively, the use of half NS may result in a decrease in serum-corrected sodium. Providers need to be vigilant toward this while using higher or lower sodium chloride when managing children with DKA. Larger trials are required to study the clinical significance of the results of this study.

Keywords

diabetic ketoacidosis, fluids, hyperchloremia, pediatrics

Introduction

A decrease in effective circulating insulin in children with type 1 diabetes mellitus may lead to life-threatening diabetic ketoacidosis (DKA), resulting in metabolic acidosis, severe dehydration, and electrolyte abnormalities. According to the American Diabetes Association (ADA) guidelines and European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society (ESPE/LWPES) Consensus Statement, rehydration should be initiated with a slow small bolus of normal saline (NS, 0.9%) followed by solutions with a tonicity of $\geq$0.45% saline (half NS) for subsequent fluid management.[1,2] There is not much evidence supporting any particular fluid; therefore, both NS and half NS are widely used in clinical practice.

We conducted a retrospective chart review with the objective of describing the effect of NS versus half NS on sodium, chloride, and acidosis in the management of DKA.

Design and Methods

Study Design

A retrospective chart review was done in all children (1 to 18 years old) admitted with the diagnosis of DKA, in the pediatric intensive care unit (PICU) between 2005 and 2010. Inclusion criteria were children between the age of 1 and 18 years with initial serum pH <7.3 and serum bicarbonate <15 meq/L with hyperglycemia and ketonuria. Exclusion criterion was patients in shock requiring pressors for management.

There were 123 children admitted with the diagnosis of DKA: 2 had septic shock (blood culture positive for methicillin-resistant *Staphylococcus aureus* requiring inotropic agents and vasopressors); therefore, 121 were included in the study. The DKA protocol at our institution was amended in 2008, which recommended NS for post-bolus rehydration. There were 69 children admitted for DKA from 2008 to

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Table 1. Demographic and Baseline Physiologic Variables. [a,b]

Demographic Variables	Group A (Normal Saline), N = 47 Mean ± SD	Group B (Normal Saline to Half Normal Saline), N = 33 Mean ± SD	Group C (Half Normal Saline), N = 41 Mean ± SD	*P* Value
Age in years, median	12.9 ± 4.1	9.9 ± 4.4	11.2 ± 4.6	.01[c]
Gender (female %)	62	61	49	NS
Mean initial bicarbonate (meq/L)	9.9 ± 3.7	9.0 ± 2.8	9.3 ± 3.7	NS
Mean initial glucose (mg/dL)	506.3 ± 164.1	617.7 ± 288.9	505.9 ± 208	.05
Mean initial osmolality (mOsm/kg)	307.8 ± 12.8	317.5 ± 27.9	312.3 ± 19.6	NS
Mean initial corrected sodium (meq/L)	139.8 ± 4.	141.6 ± 7.6	142.1 ± 6.4	NS
Mean initial chloride (meq/L)	102.1 ± 5.3	99.7 ± 7.4	103.4 ± 5.8	NS
Initial anion gap	21.30 ± 6.5	24.70 ± 5.5	22.30 ± 6.4	NS

Abbreviations: NS, not significant; SD, standard deviation.
[a] Percentages are relative to the total in each group and significance is based on chi-square test.
[b] All other variables are continuous and significance is based on 1-way analysis of variance.
[c] Statistically significant ($P < .05$).

2010: 6 received half NS and 63 received NS out of which 27 were switched to half NS at some point during insulin infusion. Out of the 52 children admitted between 2005 and 2007, 35 received half NS and 17 received NS out of which 6 were switched to half NS at some point during insulin infusion. Approval for the study was received from the local institutional review board (Springfield Committee on Research Involving Human Subjects).

Data Collection

Demographic information, length of insulin infusion and hospital stay, volume of fluid bolus, type and volume of fluid infused, total amount of sodium given, blood glucose, serum electrolytes (sodium, chloride, bicarbonate), mannitol and/or 3% sodium chloride administration, head computed tomography (CT), and outcome were obtained from the medical records.

For our study, DKA was considered resolved when serum bicarbonate was ≥18 or when insulin infusion was discontinued, whichever was achieved first. For majority of the patients, we found that plasma glucose was checked every hour; sodium, potassium, and bicarbonate every 2 hours; and serum chloride every 6 to 8 hours. We calculated corrected sodium (cNa = measured Na +0.016 [measured glucose mg/dL -100])[3] and effective osmolality (2x cNa + Glu/18) at admission, throughout the course, and at resolution of DKA. Anion gap (Na-[Cl + HCO_3]) was calculated at similar times in addition to the time of maximum serum chloride.

Patients were placed in 3 arms based on the type of fluid received: A = only NS until resolution of DKA, B = initial NS changed to half NS at some point during management, and C = only half NS until resolution of DKA.

Statistical Methods

Categorical variables (gender and proportions of hyperchloremia and anion gap) between the 3 groups were compared using chi-square test. For continuous variables, one-way analysis of variance (ANOVA) was used as an overall test to determine the presence of differences in means among the 3 groups. Tukey follow-up tests were then performed to compare pairs of means. Significance level was set at .05 for all tests. SPSS statistical software version 19.0 (SPSS Inc, an IBM Company, Armonk, NY) was used for data analyses.

Results

In all, 47 patients in group A (NS alone), 33 patients in group B (NS changed to half NS), and 41 patients in group C (half NS alone) met the inclusion criteria. Baseline variables, except initial serum glucose, were similar in the 3 groups (Table 1).

Although total fluid received (Table 2) was similar in all the groups ($P > .1$), total sodium received by the NS groups A and B was significantly higher than half NS group C (mean 13.2 meq/kg/d ± 4.2 and 13.1 ± 4.2 vs 7.1 ± 2.6, respectively; $P < .01$). There was no difference between groups A and B ($P = .91$).

In the half NS group C, corrected serum sodium (Tables 2 and 3) decreased by a mean of 2.3 ± 5.5 mEq/L from admission to resolution of DKA, when compared to its increase in both NS groups A and B (mean increase 1.2 ± 4.1 and 2.2 ± 4.5, respectively; $P < .01$). Change was similar in groups A and B ($P = .33$).

The fall in effective serum osmolality from admission to resolution of DKA was greater in the half NS group C when compared to NS group A (mean 23.9 ± 15.7 mOsm/kg vs 16.2 ± 13.2, respectively; $P = .02$; Tables 2 and 3). The rate of change in glucose was similar in all the 3 groups.

The NS groups A and B had higher proportion of hyperchloremia (serum chloride >109 meq/L) at some point during management of DKA than half NS group C (64% and 79% versus 32%, respectively; $P < .01$; Tables 2 and 3). This hyperchloremia resulted in a significantly higher incidence of non-anion gap acidosis in groups A and B when compared to group C (53% and 73% vs 22%, respectively; $P < .01$). Bicarbonate was similar in all the 3 groups at resolution of DKA ($P = .35$).

The PICU stay (time to resolution of DKA) was longer in NS group B than in half NS group C (mean 16.8 hours ± 7.1

Table 2. Summary of Outcomes Based on Fluids of Different Tonicity.[a,b,c]

Outcome Variables	Group A (Normal Saline), N = 47	Group B (Normal Saline to Half Normal Saline), N = 33	Group C (Half Normal Saline), N = 41	*P* Value
Mean PICU length of stay, hours	14.7 ± 7.5	16.8 ± 7.1	12.7 ± 6.9	.056
Total fluid, mL/kg/h	3.6 ± 1.2	4.0 ± 1.1	3.9 ± 1.4	NS
Total Na, meq/kg/d	13.2 ± 4.2	13.1 ± 4.2	7.1 ± 2.6	<.01[d]
Total NS bolus, mL/kg	19.2 ± 9.7	24.7 ± 11.8	21.3 ± 11.0	NS
Difference in corrected Na (Final − initial), meq/L	1.2 ± 4.2	2.2 ± 4.5	−2.3 ± 5.5	<.01[d]
Rate of change of glucose, mg/dL/h	27.3 ± 18.4	31.6 ± 26.0	35.0 ± 29.0	NS
Difference in corrected osmolality (initial − final), mOsm/kg	16.2 ± 13.2	20.0 ± 17.3	23.9 ± 15.7	.07
Hyperchloremia, n	30 (63.8%)	26 (78.8%)	13 (31.7%)	<.01[d]
Nonanion gap acidosis with hyperchloremia, n	25 (53.2%)	24 (72.7%)	9 (22.0%)	<.01[d]
Final anion gap	11.9 ± 3.0	11.8 ± 4.5	12.8 ± 2.7	NS
Maximum chloride	110.85 ± 4.77	114.85 ± 7.31	108.61 ± 5.33	<.01[d]
Anion gap at maximum chloride	11.8 ± 3.0	11.7 ± 3.2	15.1 ± 3.6	<.01[d]

Abbreviations: Na, sodium; PICU, pediatric intensive care unit.
[a] Percentages are relative to the total in each group and significance is based on chi-square test.
[b] All other variables are continuous and significance is based on 1-way analysis of variance.
[c] Follow-up Tukey test for pairwise comparisons between the 3 groups is reported in Table 3.
[d] Statistically significant ($P < .05$).

Table 3. Significance (*P* Values) of Pairwise Comparison of Outcomes Between Fluids With Different Tonicity.[a,b]

Outcome Variables	Group A Versus B	Group B Versus C	Group C Versus A
Mean PICU length of stay, hours	.21	.02[c]	.19
Total fluid, mL/kg/h	.10	.67	.28
Total Na, meq/kg/d	.91	<.01[c]	<.01[c]
Total NS bolus, mL/kg	.93	.84	.88
Difference in corrected Na, meq/L	.31	<.01[c]	<.01[c]
Rate of change of glucose, mg/dL/h	.42	.60	.15
Difference in corrected osmolarity, mOsm/kg	.29	.33	.02[c]
Hyperchloremia, n	.15	<.01[c]	<.01[c]
Acidosis with hyperchloremia, n	.08	<.01[c]	<.01[c]
Final anion gap	.94	.27	.12
Maximum chloride	<.01[c]	<.01[c]	.04[c]
Anion gap at maximum chloride	.81	<.01[c]	<.01[c]

Abbreviations: Na, sodium; PICU, pediatric intensive care unit.
[a] Group A (normal saline), group B (normal saline changed to half normal saline), group C (half normal saline).
[b] The level of significance is referred to the Tukey follow-up test for continuous variables and chi-square test for percentages.
[c] Statistically significant ($P < .05$).

vs mean 12.7 hours ± 6.9; $P = .02$). Although it was longer in NS group A (mean 14.74 hours ± 7.51) when compared to group C, it was not statistically significant (Tables 2 and 3). The NS was changed to half NS in group B at a mean of 10 ± 1.4 hours after post-bolus rehydration was initiated.

All patients were discharged home with baseline pre-DKA neurological status. None of the patients received mannitol in the half NS group. One received mannitol in NS group A, who did well later. One other patient had brain imaging done in group A for encephalopathy but improved without any specific management for cerebral edema (CE). None of the patients received 3% sodium chloride.

Discussion

We present the results of a retrospective study done to determine the effect of post-bolus rehydration fluid consisting of NS versus half NS in the management of DKA. All children received similar volumes of fluid boluses and total fluid until the resolution of DKA. However, the total sodium received was much less in the half NS group which led to a greater drop in the corrected serum sodium. Rate of change of glucose was similar in all the 3 groups. Therefore, the greater drop in serum osmolality in the half NS group can be attributed to the drop in corrected serum sodium.

The rationale for the recommendation of half NS in the management of DKA is avoidance of CE.[2] Although there are conflicting studies demonstrating that there may be no role of sodium content of the intravenous (IV) fluid in the development of CE,[4] one of the widely accepted risks for CE is the attenuated rise in corrected serum sodium resulting in rapid drop in effective serum osmolality.[5-8] Our study shows that use of half NS alone as post-bolus rehydration fluid may actually result in a decrease in corrected serum sodium during the management of DKA.

There are postoperative studies, in adults, suggesting that hyperchloremia with acidosis can occur when large volume of NS is used during anesthesia and surgery.[9-11] Similarly, resuscitation with NS can cause hyperchloremic acidosis in infants and children with diarrhea and septic shock.[12,13]

A recent study in adults in the emergency department suggests that resuscitation of DKA with NS for 4 hours when compared to a balanced electrolyte solution can result

in hyperchloremia.[14] Hyperchloremia and nonanion gap acidosis can also occur in DKA during the recovery phase because of loss of bicarbonate and renal retention of sodium chloride.[15-18] Our study shows that the use of NS potentiates this effect because of addition of increased chloride infusion. There was significant hyperchloremia in the NS group and the group that was changed from NS to half NS. This led to nonanion gap acidosis and the need to change to half NS in the latter group. This also, most likely, resulted in an increased duration of insulin infusion and correction of DKA necessitating prolonged PICU stay. This could be explained by the assumption that the acidifying effect of hyperchloremia can be interpreted erroneously as ongoing ketoacidosis leading to prolongation of management of DKA.[18] Based on this study, we have actually modified our management protocol incorporating procedures to make physicians vigilant toward hyperchloremia and resulting nonanion gap acidosis.

To our knowledge, our retrospective review is the only study comparing NS versus half NS as post-bolus rehydration fluid for managing children with DKA admitted to the PICU. Although this study was not done with the aim to study the association of CE with fluids of various tonicity (because of the small sample size), imaging and hyperosmolar therapy for suspicion of CE were included in the data collection. Only 2 children in the NS group A (1 received mannitol and 1 had a head CT done) were suspected to have CE. All patients went home with baseline pre-DKA neurologic status.

The retrospective nature of our study is its biggest limitation. Nevertheless, baseline demographic and physiologic variables were similar. The management protocol used was the same except for a change to NS for post-bolus rehydration in 2008. This reduces management bias and strengthens the validity of the results. Another limitation is the small sample size. However, the number of patients represents a sufficient size for our study end point: calculations of fluid, electrolyte, and osmolarity. We did not aim to study the association of NS versus half NS with CE or mortality. This would require a much larger study.

In conclusion, hyperchloremia-associated nonanion gap acidosis can occur when NS is used as post-bolus rehydration fluid in the management of DKA in children, which, if not monitored carefully, could result in an increase in insulin infusion duration and ICU stay. Alternatively, cNa may decrease with a more rapid decrease in effective serum osmolarity when half NS is used, which could result in increased risk of CE. Providers need to be vigilant toward the risks and benefits of using higher or lower sodium chloride solutions while managing DKA. A larger prospective randomized trial of NS versus half NS with sufficient sample size and end point of imaging proven CE and/or mortality is required to study the clinical significance of the results of our study. Additionally, a study comparing the balanced electrolyte solutions to saline solutions should be done to see whether hyperchloremia leading to nonanion gap acidosis can be avoided in the recovery phase of DKA while the cNa is maintained.

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Declaration of Conflicting Interests

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Outcome of the use of 0.9% saline versus 0.45% saline for fluid rehydration in moderate and severe diabetic ketoacidosis in children

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Abstract

Background: The debate for the optimum sodium concentration in the rehydration solution in diabetic ketoacidosis (DKA) persists till the moment. The aim was to compare the outcome of 0.9% saline versus 0.45% saline in children with moderate and severe (DKA) regarding the effect on serum electrolytes, duration of DKA resolution and the incidence of hyperchloremia.

Results: A retrospective analysis of 121 children with moderate or severe DKA was done. After the initial 4 h in which both groups received normal saline, patients were divided into two groups continuing on 0.9% (*N*=72) or switched to 0.45% saline (*N*=49). Serum chloride and Cl/Na ratios were significantly higher in 0.9% saline group at 4 and 8 h. The 0.9% saline group had significantly higher proportion of hyperchloremia at 4 and 8 h (*P* value: 0.002, 0.02). The median duration of correction of DKA (14 h among 0.9% saline versus 10 h among 0.45% saline) without significant difference (*P* value= 0.43). The change in plasma glucose, effective osmolarity, corrected Na levels were comparable between groups.

Conclusion: There is an unavoidable iatrogenically induced rise in serum chloride with higher incidence of hyperchloremia with the use of normal saline in rehydration of children presenting in DKA and shock. The use of 0.45% saline as post-bolus rehydration fluid is not associated with a decline in the corrected serum sodium concentration and does not affect the rate of correction of acidosis or rate of drop in blood glucose or duration of DKA resolution when compared to normal saline.

Keywords: DKA, Hyperchloremia, 0.45% saline, Normal saline, Rehydration

Background

Diabetic ketoacidosis (DKA) is an earnest acute complication of type one diabetes which can occur at any age, often can occur at the onset of disease or in the already diagnosed patients due to discontinuation of insulin or improper sick day management [1]. The goal of all existing DKA management protocols to do instantaneous fluid replacement to correct the intracellular dehydration and the ongoing electrolytes losses [2]. The fluid replacement must be prompt but very careful to avoid the cerebral edema [3]. Cerebral edema is known to be the leading cause of death in diabetic ketoacidosis (DKA) and the treatment centers around avoiding this complication of management [4]. Argument is still present regarding the type, amount, and rate of intravenous (IV) replacement fluid therapy. International Society for Pediatric and Adolescent Diabetes (ISPAD), 2018

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consensus guidelines advise that after the initial resuscitation, fluids used may be in the form of solution with tonicity ranging between 0.45 and 0.9% according to the clinical evaluation of the patients [2], but till now based on the present evidence there is no particular treatment strategy preferable than the other [5].

The rationale for the use of half NS is to minimize the risk of cerebral edema through declined rise in corrected serum sodium and drop in effective serum osmolality [6].

The normal saline (0.9%) is the most appropriate physiological solution used for the initial rehydration however it carries the risk of increasing the chloride load which results in development of hyperchloremic metabolic acidosis [7]. Hyperchloremic metabolic acidosis (DKA) may be observed during management and is caused either by urinary loss of bicarbonate precursors as ketones and/or iatrogenically from chloride administration in rehydration fluids [8]. The acidifying effect of chloride was blamed in masking the resolution of DKA [9]. With the shortage of availability of costly laboratory investigations (such as β-hydroxybutyrate) in many developing countries identifying the cause of protracted metabolic acidosis in DKA patients is not always feasible. In the current study we aimed to compare the outcome of using 2 different concentrations of sodium in the rehydration fluids (0.9% NS versus 0.45% saline) in moderate and severe DKA with regards to the effect on serum electrolytes, effective osmolarity, duration of DKA resolution, the incidence of hyperchloremia.

Methods

Participants

This is a retrospective cohort study included 49 children 1–15years with moderate or severe DKA who received rehydration solution using 0.45% saline at intermediate care unit of Diabetes, Endocrine, and Metabolism Pediatric Unit (DEMPU), Children's Hospital over the period from August to October 2016. This was compared to historical cohort of 72 patients with moderate and severe DKA who received 0.9% saline as rehydration solution at the same unit during the preceding period from March to July 2016.

DKA was defined as having blood glucose >200 mg/dL (11.4 mmol/L), a venous pH <7.30 or a plasma bicarbonate level <15 mmol/L, and ketonemia or ketonuria and arterial blood gases (ABG) showed moderate DKA if arterial pH >7.1 and <7.2 with bicarbonate <10 and >5mmol/L or severe DKA if arterial pH <7.1, bicarbonate <5 mmol/L [10]. Patients were excluded if they had (1) any neurological abnormality or Glasgow Coma Scale (GCS) <13, (2) received any therapy (HCO3, mannitol, fluid, insulin) before admission to our hospital or were referred after the first 4 h of management, (3) any cause of acidosis other than DKA, (4) corrected serum sodium ≤130 and≥150 mmol/l.

Data on age, sex, onset of diabetes whether newly diagnosed or known, duration of diabetes, precipitating factor for DKA development, duration of insulin infusion, dose of insulin infusion, volume of fluid infused, and the use of bicarbonate therapy were collected.

All patients included in the study were managed according to ISPAD guidelines for DKA treatment [2] which is the protocol adopted at our unit which allow consistency concerning treatment. The protocol adopted at our unit as follows:

All included patients were managed accordingly: immediate measurement of blood glucose and capillary BHOH using glucometer (Free style Optium, Abbott)[1] were performed when available, weighing the patient and assessment of level of consciousness according to Glasgow Coma Scale [11] and severity of dehydration, full examination for a precipitating factor, and laboratory investigations

Subsequent clinical and biochemical monitoring included hourly assessment of vital signs, hourly (or more frequently as indicated) neurological observations (GCS) for warning signs and symptoms of cerebral edema, hourly capillary blood glucose concentrations, measurement of serum glucose, Na, K, CL, BUN, creatinine, and blood gases at the time of admission and every 4 h till DKA resolution. N.B. Blood glucose was measured in mg/dl, where 1mg/dl=18mmol/L.

- Calculation of:
  - Anion Gap using the following formula: (Na+) − (HCO3- + Cl-). Normal= 12 ± 2 mmol/L
  - Corrected Na =Measured Na+2(blood glucose −100)/100
  - Serum osmolality (mosmol/kg); effective: 2 (Na) + glucose/18 [12].
  - Hyperchloremia is defined as ratio of chloride: sodium [Cl−: Na+] > 0.79 [13].
- Fluid therapy
  A. Resuscitation fluid (0.9% saline) was used for restoration of the peripheral circulation. The volume administered is 10 ml/kg over 1–2 h, this bolus fluid is given to patients with severe volume depletion and may be repeated until tissue perfusion is adequate. However, shocked patients with impaired peripheral perfusion were given 20 ml/kg as rapidly as possible.

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B. Deficit replacement fluid therapy: First 4 h 0.9% saline was used then fluid with tonicity either 0.45% saline (half NS) or 0.9% saline was used.
C. Patients were divided into two groups according to the type of rehydration fluid used after 4 h: group 1 (N=72): Rehydration solution using 0.9% saline; group 2 (N=49): Rehydration solution using 0.45% saline provided that those patients had normal Na concentration.
The volume of total fluid replacement therapy and its rate were calculated based on data from Darrow study [2, 14].
D. Glucose 10% was added to replacement fluids (ratio 1:1) when plasma glucose reached approximately 300 mg/dL or if the rate of blood glucose dropped very rapidly (>88 mg/dL/h) after initial fluid expansion.
E. Potassium replacement was initiated after measurement of its serum level at concentration of 40 meq/L after initial volume expansion and concurrent with starting insulin therapy. If the patient was hyperkalemic, potassium replacement therapy was postponed until urine output was documented.
F. Bicarbonate therapy was considered in cases of severe acidosis (PH<6.9) with life threatening cardiac decompensation and also indicated in cases of life threatening hyperkalemia. It is given intravenously at a dose of 1–2 meq/kg over 1 h.
G. Cerebral edema: monitoring of clinical symptoms and signs suggestive of development of cerebral edema (headache, deterioration of neurological status, development of any neurological deficit, convulsion, Cushing's triad) is a crucial part of DKA management. Once clinically suspected, immediate management is initiated. The rate of rehydration fluid is adjusted to maintain good perfusion and normal blood pressure while avoiding overhydration. Hypertonic solution (mannitol or hypertonic saline) is given slowly over 10–15 min. Other measures to decrease intracranial pressure must be applied (elevation of the head 30°, intubation with hyperventilation if patient had severe deterioration of neurologic status).

- Insulin therapy

Insulin infusion was started after 1 h of initiation of volume expansion by fluid replacement therapy at a dose ranging from 0.05 U to 0.1 U/kg/h. Criteria for shifting to subcutaneous insulin included resolution of acidosis (PH ≥ 7.3, HCO3≥15 mEq/L), a good general condition and hemodynamic stability, tolerating oral intake, patient no longer on vasopressors and BOHB ˂ 3 mmol/L.

The study protocol received approval from our Institutional Research Ethics Committee.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median and range for numerical variables or frequencies, and percentages for categorical variables. Comparison of numerical variables between the study groups was done using Student's T test. For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

The total number of included patients was 121 participants. They were divided into two groups according to the type of rehydration fluid used after 4 h: group 1 (0.9% saline) included 72 participants and group 2 (0.45% saline) included 49 participants. Clinical characteristics and initial biochemical parameters at admission are illustrated in Table 1.

Our patients were 65 females (53.7%) and 56 males (46.3%), their ages ranging from 1 to 14 years and all patients were neurologically free with GCS>13. The patients were divided according to the degree of dehydration at presentation into moderate dehydration 27 patients (22.3%) and severe dehydration 94 patients (77.7%). Of the whole group, 55 patients were known to have diabetes (45.5%) while for 66 patients (54.5%) DKA was their first presentation. Concerning the severity of DKA, 49 patients had moderate DKA while 72 patients had severe DKA. Corrected sodium levels of our patients at presentation and after 4 h (at time of change of fluid) ranged from 135 to ≤ 150 and their ABG correlated with the criteria of moderate and severe DKA. BHOH at presentation ranged from 3.1–8.3 mmol/L. The duration of correction of ketoacidosis among the whole group ranged from 6 to 40 h.

The age of participants of both groups was comparable, the median age of normal saline NS (group 1) was 8 years (range, 1–13) while that of group 2 (half normal saline) was 7 years (1–14) P value=1.000. The number (%) of patients in NS group who had new onset T1DM was 47/72 (58.3%) compared to 24/49 (49%) in the other group, the difference was not significant P value=0.59.

Table 1 Demographic and baseline biochemical variables at time of admission

Parameters	Group 1 (0.9%) (*N*=72)	Group 2 (0.45%) (*N*=49)	*P* value
Age (years) (mean ± SD)	7.11 ± 3.77	7.39 ± 3.87	0.69
Sex *n* (%)			
Male	39 (45.8%)	17 (34.7%)	**0.03**
Female	33 (54.2%)	32 (65.3%)	
Degree of dehydration *n* (%)			
Moderate	17 (23.6%)	10 (20.4%)	0.43
Severe	55 (76.4%)	39 (79.6%)	
DKA presentation *n* (%)			
Newly diagnosed	42 (41.7%)	24 (51%)	0.59
Known to have diabetes	30 (58.3%)	25 (49%)	
Shock therapy (ml/kg) *n* (%)			
No	15 (20.8%)	25 (51%)	**0.001**
10 ml/kg	15 (20.8%)	3 (6.1%)	
20 ml/kg	19 (26.4%)	4 (8.2%)	
30 ml/kg	23 (31.9%)	17 (34.7%)	
Rate of fluids (maintenance + deficit) ml/kg/h (mean ± SD)	99.93 ± 26.88	94.16 ± 31.13	0.34
Actual fluid intake (L) (median)	4.73	4.45	0.39
Patients received bicarbonate therapy	13 (18.1%)	11 (22.4%)	0.36
Mean insulin dose (IU/kg/h) mean ± SD			
1st 6 h	0.11 ± 0.02	0.1 ± 0.01	0.80
After 1st 6 h	0.11 ± 0.03	0.1 ± 0.02	0.48
Duration of DKA resolution (hours) (median, range)	14 (6–40)	10 (6–38)	0.43
Glucose (mg/dl) (mean ± SD)	532.67 ± 157	550.14 ± 139.64	0.53
Serum Na (meq/L) (mean ± SD)	133.58 ± 4.56	134.16 ± 4.24	0.47
Corrected Na (meq/L) (mean ± SD)	142.4 ± 4.54	143.12 ± 4.75	0.40
Serum CL(meq/L) (mean ± SD)	102.67 ± 5.02	102.91 ± 4.49	0.81
CL:Na ratio (mean ± SD)	0.77 ± 0.03	0.77 ± 0.18	0.97
BHOB (mmol/L) (mean ± SD)	5.44 ± 1.13	5.43 ± 1.55	0.95
PH (mean ± SD)	7.08 ± 0.099	7.06 ± 0.12	0.39
HCO3 (meq/L) (mean ± SD)	5.8 ± 2.5	6 ± 2.7	0.65
Anion gap (mean ± SD)	25.9 ± 4.4	24.6 ± 3.5	0.12
Creatinine (mg/dl) (mean ± SD)	0.75 ± 0.24	0.76 ± 0.31	0.81
Effective osmolality (mosmol/L) (mean ± SD)	297.1 ± 11.9	300.9 ± 11.3	0.07
Severity of DKA *n* (%)			
Moderate (*n*=49)	29 (40.3%)	20 (40.8%)	0.95
Severe (*n*= 72)	43 (59.7%)	29 (59.2%)	

Precipitating factors for DKA were similar in both groups with infections representing 46.7% in NS group and 44% in 0.45% saline. There was no discernible precipitant in 46.7% of NS group and none in 52% of the other group.

Significantly more patients in the NS group needed shock therapy (79.2% versus 49% in 0.45 saline group, *P*=0.001). Rates of fluids, total fluid intake, severity of DKA, mean insulin doses/hour, and number of patients needing sodium bicarbonate were comparable (Table 1).

The initial laboratory data at the time of recruitment (serum glucose, corrected serum Na, serum Cl, Cl:Na ratio, PH, HCO3, creatinine, effective osmolarity, and anion gap) were comparable between two groups (Table 1). Corrected serum sodium was comparable in both groups throughout the study period. Serum chloride and Cl/Na ratios were significantly higher in NS group at 4 and 8 h after initiation of therapy. Serum chloride levels rose significantly by 2.1 mmol/L between hour 4 and hour 8 in NS group (*P*=0.007) and by 1.7mmol/L in 0.45% group (*P*=0.37). The NS group (I) had significantly higher proportion of hyperchloremia at 4 and 8 h (*P* value, 0.002, 0.02 respectively). On the other hand, the anion gap was significantly higher at 4 and 8 h in 0.45% saline-receiving patients with (*P* values, 0.006, 0.000 respectively). At the start, BHOH levels in both groups had a mean value of 5.5 ± 1.1 vs 5.4 ± 1.5 (*P* value=1.000). Differences continued to be insignificant throughout the study period (Table 2). Concerning the course of blood glucose during correction, there was no significant difference between two groups at 4 and 8 h (*P* value=0.45, 1.00 respectively). Effective serum osmolarity was comparable during the study period. Figures 1, 2, 3 and 4 show blood chloride, glucose, anion gap, and bicarbonate trends in the two groups throughout the study period.

Table 2 The course of PH, HCO3, corrected Na, CL, Cl:Na ratio, capillary BHOB, anion gap, glucose, and effective osmolarity at 4 and 8 h among both groups

Laboratory variables	Timing (hours)	Group 1 0.9% NS (*N*=72) Mean ± SD	Group2 0.45% NS (*N*=49) Mean ± SD	*P* value
PH	**4**	7.16 ± 0.1	7.14 ± 0.13	0.37
	8	7.23 ± 0.09	7.20 ± 0.1	0.55
	At recovery	7.35 ± 0.04	7.36 ± 0.05	0.21
HCO3 (meq/L)	**4**	7.34 ± 3.4	6.98 ± 3.18	0.56
	8	9.8 ± 3.6	8.8 ± 3.5	0.5
	At recovery	16.9 ± 1.37	17.02 ± 1.96	0.82
Serum Na (meq/L)	**4**	136.28 ± 4.94	135.94 ± 4.64	0.70
	8	137.3 ± 5.4	138.4 ± 6.6	0.98
	At recovery	140.7 ± 6.5	140.3 ± 5.4	0.69
Corrected Na (meq/L)	**4**	142 ± 4.8	143.1 ± 4.6	0.18
	8	141 ± 6	143.4 ± 6.2	0.12
	At recovery	140.7 ± 6.5	140.3 ± 5.4	0.69
CL (meq/L)	**4**	106.28 ± 5.1	103 ± 3.6	**0.002**
	8	108.4 ± 5.6	104.7 ± 6.1	0.06
CL:Na ratio	**4**	0.78 ± 0.03	0.76 ± 0.02	**0.001**
	8	0.79 ± 0.02	0.76 ± 0.03	**0.000**
Anion gap	**4**	22.8 ± 5.1	26.1 ± 5	**0.002**
	8	18.5 ± 4.5	25.8 ± 5.6	**0.000**
BHOH	**4**	4.6 ± 1.1	4.9 ± 1.5	0.97
	8	4.05 ± 1.1	4.09 ± 1.4	0.88
Plasma glucose (mg/dl)	**4**	389 ± 166	433 ± 145	0.35
	8	307.3 ± 134	324.8 ± 124.5	0.51
Effective serum osmolality (mosmol/L)	**4**	293 ± 12.4	296 ± 12.7	0.21
	8	291 ± 12.5	295 ± 13	0.22
Hyperchloremia *n* (%)	**0**	9 (15.3%)	4 (11.1%)	0.4
	4	16 (28.6%)	2 (4.9%)	**0.002**
	8	15 (34.9%)	4 (12.5%)	**0.02**

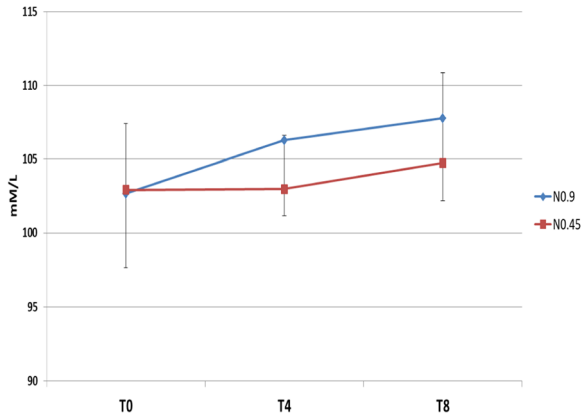

Fig. 1 Mean ± SD of serum chloride (mmol/L) in NS 0.9 and saline 0.45 groups over the study period

Although the median duration of correction of ketoacidosis was longer among normal saline group than 0.45% saline (14 versus 10 h), it did not reach statistically significant difference (*P* value= 0.43). None of recruited patients developed brain edema or renal dysfunction. All recruited patients were discharged without any alteration in their neurological status compared to the previous status before DKA development.

Comparison between patients who did not receive any shock therapy in both groups (0.9% versus 0.45%) was shown in Table 3. The comparison revealed statistically significant difference between both groups regarding CL:Na ratio and anion gap at 8 h (*P* values, 0.007, 000) respectively. However, the other compared parameters did not show significant difference.

Discussion

The management of DKA should be aimed at restoration of normal homeostasis and tissue perfusion with a gradual reduction of acidosis and blood glucose to avoid possible complications. Isotonic (normal saline NS) is the fluid most commonly used for resuscitation initiation of rehydration during DKA management in pediatric and adult guidelines. Recently, however, there has been increasing awareness that the non-physiological nature can lead to hyperchloremic metabolic acidosis and acute renal injury as a result of renal vasoconstriction [15]. Other investigators have not found a detrimental effect of NS on overall mortality or renal functions [16]. The debate for replacing NS by other solutions with different Na concentrations persists till the moment. In our study, we compared the use of two solutions in the rehydration of children with moderate and severe DKA (NS which contains Na 154 meq/L) and (0.45% NS which contains Na 75 meq/L).

In the current study, the serum bicarbonate level and PH were comparable between both groups at the time of start of management and throughout the study with no significant difference between both groups. This is in agreement to what reported by Savas-Erdeve et al. that the use of an isotonic solution did not create a difference in HCO3 or PH levels when compared to hypotonic solution with lower Na concentration [3].

The primary cause of acidemia in DKA is thought to be ketoacidosis, lactic acidosis, and renal dysfunction can be contributing factors [13]. Hyperchloremia predominates instead in the recovery phase. Misinterpretation of hyperchloremic acidosis may obscure the detection of ketoacidosis resolution [8]. A simple bedside test with detection of BOHB levels can solve the

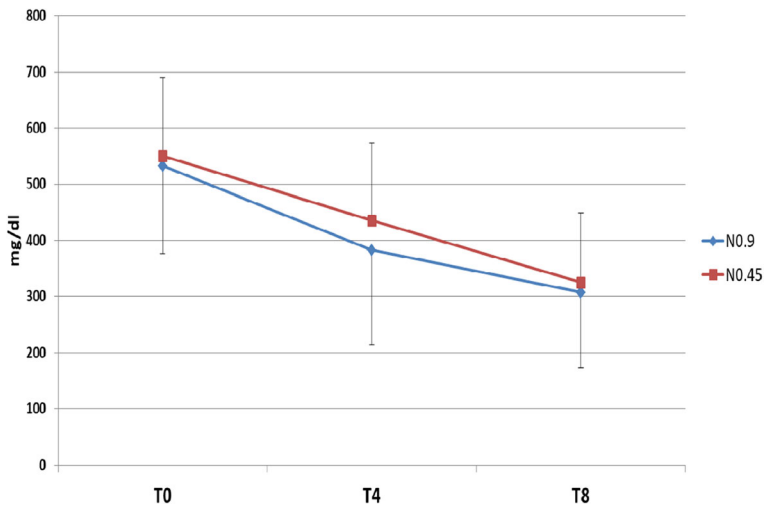

Fig. 2 Mean ± SD of serum glucose (mg/dl) in NS 0.9 and saline 0.45 groups

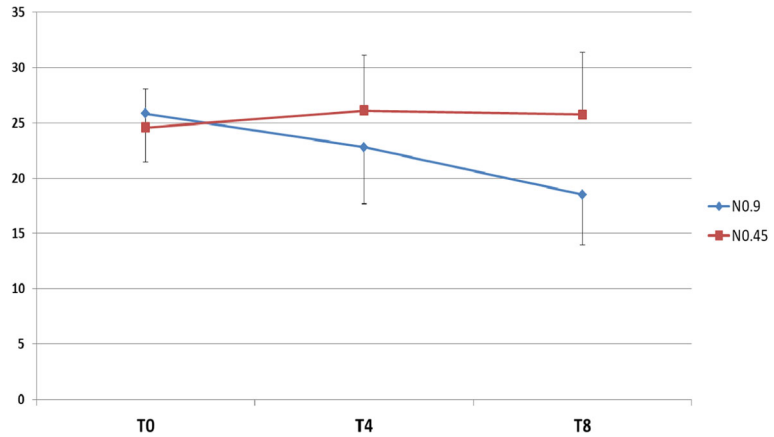

Fig. 3 Mean ± SD of anion gap in NS 0.9 and saline 0.45 groups over the study period

problem, unfortunately this test is not always available in limited resource settings. Although both groups of patients in our study presented with comparable chloride levels (102.7 vs 102.9mmol/L) on admission, differences became evident as early as 4 h into the study when both groups had been receiving NS and before rehydration fluids for the second group were changed (106.3 vs 103mmol/L). It is important to note that more patients in group 1 had received anti-shock treatment with NS boluses (79.2% vs 49%) and this had already impacted on their serum chloride levels. Additionally, comparison between patients who did not receive any shock therapy in both groups (0.9% versus 0.45%) revealed no significant difference regarding chloride levels. Previous studies have found the highest chloride levels to occur with periods of rapid rehydration with large amounts of normal saline [17]. However, anti-shock treatment can be lifesaving in some situations for restoring perfusion and improving glomerular filtration.

Eight hours into the study (4 h after group 2 had been switched 0.45% saline) serum chloride levels had climbed a further 2.1mmol/L in group 1 and 1.7mmol/L in group 2 (108.4 vs 104.7mmol/L). The NS group had significantly higher proportion of patients with hyperchloremia at 4 and 8 h. Concerning the chloride, sodium ratio, the NS group had significantly higher ratio at 4 and 8 h than those in the 0.45% saline group. In contrast, such frequency of patients with hyperchloremia was not seen in the 0.45% NS group which suggests that the choice of rehydration fluid might be an important factor for the development of hyperchloremia. This comes in line with several studies that showed that patients who received normal saline had significantly higher incidence of hyperchloremic acidosis [18–20].

The median duration of management till DKA resolution was longer among the group of NS (14 h) versus (10 h) among 0.45% saline group but it did not reach statistical significance (*P* value=0.43). We speculate that

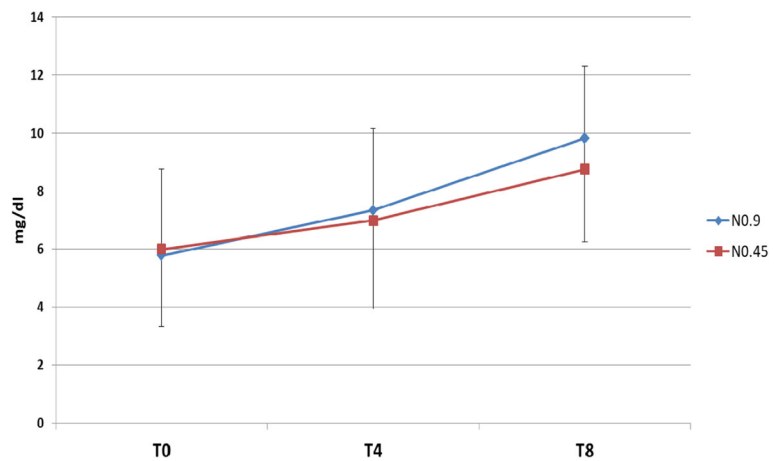

Fig. 4 Serum HCO3 (mmol/L) in NS 0.9 and saline 0.45 groups over the study period

Table 3 Comparison between patients who did not receive shock therapy in both groups (0.9% versus 0.45% saline) regarding different laboratory parameters

Laboratory variables	Timing (hours)	Group 1 0.9% NS (*N*=15) Mean ± SD	Group2 0.45% NS (*N*=25) Mean ± SD	*P* value
PH	**0**	7.14 ± 0.07	7.13 ± 0.06	0.60
	4	7.21 ± 0.09	7.22 ± 0.05	0.62
	8	7.29 ± 0.09	7.26 ± 0.04	0.42
	12	7.32 ± 0.04	7.34 ± 0.04	0.56
HCO3 (meq/L)	**0**	8.4 ± 1.6	8.02 ± 1.8	0.49
	4	10.05 ± 2.8	9.41 ± 2.1	0.42
	8	13.3 ± 3.01	11.4 ± 1.9	0.07
	12	13.25 ± 2.8	12.6 ± 1.3	0.67
Serum Na (meq/L)	**0**	133.8 ± 3.8	134 ± 4.2	0.85
	4	136.3 ± 5.7	135.4 ± 5.3	0.62
	8	136.3 ± 4.6	136.3 ± 6.6	0.98
Corrected Na (meq/L)	**0**	141.8 ± 4.7	142 ± 4.6	0.91
	4	140.8 ± 5.2	142.3 ± 5.1	0.37
	8	141.1 ± 6.1	136.3 ± 4.6	0.40
CL (meq/L)	**0**	102.4 ± 4.9	102.7 ± 4.3	0.86
	4	104.7 ± 3.8	102.6 ± 3.5	0.12
	8	107.6 ± 4.8	103.6 ± 4.2	0.08
CL:Na ratio	**0**	0.77 ± 0.03	0.76 ± 0.02	0.94
	4	0.76 ± 0.01	0.75 ± 0.02	0.21
	8	0.79 ± 0.01	0.76 ± 0.03	**0.007**
Anion gap	**0**	23.6 ± 2.9	22.8 ± 2.9	0.48
	4	21.4 ± 5.02	23.7 ± 4.03	0.16
	8	13.8 ± 2.03	11.4 ± 1.9	**0.000**
BHOH	**0**	4.8 ± 0.94	5.32 ± 1.6	0.26
	4	3.9 ± 1.1	4.2 ± 1.3	0.48
	8	3.07 ± 0.88	3.4 ± 1.	0.43
Hyperchloremia *n* (%)	**0**	2 (13.3%)	2 (8%)	0.63
	4	2 (13.3%)	1 (4%)	0.22
	8	2 (13.3)	2 (8%)	0.63
Duration of DKA resolution (hours)		9.87 ± 3.58	8.80 ± 3.317	0.34

the prolonged duration of insulin infusion among normal saline group due to misinterpretation of hyperchloremic acidosis as ongoing ketoacidosis but unfortunately lack of availability of chloride levels after 8 h was a limitation in this study.

Basnet et al. found hyponatremia to be induced in patients receiving 0.45% from the start of DKA management. This did not occur in patients switching to 0.45% after an initial period of NS treatment [18]. Our findings concur with those of that study since we found no significant differences in serum sodium levels between the two groups throughout the course of DKA management. This is also in line with Rother et al. who found that rehydration using 75 mmol/L of Na did not lead to decline in the serum Na level [21]. However, this contradicts Toledo et al. who reported a higher plasma Na level with the use of an isotonic perfusate than that achieved with a perfusate with a lower Na content [22]. Savas-Erdeve et al. did not find any difference in plasma Na and plasma corrected Na between patients who received rehydration solutions containing 75mEq/L and patients received 100 mEq/L of Na. Gosmanov et al. recommend in adult DKA management that if patients are to be switched to 0.45% saline after an initial 4-h resuscitation

with NS, patients must be both hemodynamically stable and have a normal to high corrected serum sodium level. If patients subsequently become hyponatremic, treatment should revert to NS [23].

Concerning the course of glycemia, the initial glucose level and its rate of decline did not show any significant differences between the two studied groups. This is noted also in other studies using rehydration solutions with different Na concentrations [3, 18, 20]. In addition, there was no significant difference between the two studied groups as regards the rate of insulin infusion. This is in line with what was reported by Yung et al. [20]. This denotes that insulin infusion dose is not affected by the change in Na concentration in the rehydration fluids during DKA management.

Capillary BHOH levels did not differ between the two groups throughout the study period but the anion gap dropped faster in the group receiving NS, significantly lower levels being demonstrable as early as 4 h into the management of DKA. It is speculated that since BHOH levels were equal in both groups throughout, it was the higher levels of serum chloride in the NS patients that narrowed the gap in this group.

Limitations of the study

The retrospective nature of the study is the main limitation. Future prospective studies with larger number of participants with more emphasis on determination of brain injuries associated with DKA management and its risk factors are needed.

Conclusion

There is an unavoidable iatrogenically induced rise in serum chloride with the use of normal saline in the initial resuscitation of children presenting in DKA and shock. The incidence of hyperchloremia is significantly less with the use of half normal saline. Half normal saline is not associated with a decline in the corrected serum sodium concentration and does not affect the rate of correction of acidosis or rate of drop in blood glucose or duration of DKA resolution when compared to normal saline solution as post-bolus rehydration fluid therapy in pediatric patients with DKA.

Abbreviations

DKA: Diabetic ketoacidosis; IV: Intravenous; ISPAD: International Society for Pediatric and Adolescent Diabetes; DEMPU: Diabetes, Endocrine, and Metabolism Pediatric Unit; GCS: Glasgow Coma Scale; ABG: Arterial blood gases; BHOH: β-Hydroxybutyrate; NS: Normal saline

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Authors' contributions

Dr. MH shared in study design, interpretation of data, statistical analysis, drafting and writing manuscript, and final revision of the version to be published. Dr. NB revised the results and participated in writing the manuscript, Dr. HSE did the laboratory work up, Dr. MI was the consultant who directly oversaw the progress of the cases, Drs. HM and SA shared in design of study, data collection, interpretation of data, drafting of the article, and final revision for publication. Dr. NA participated in data collection and sorting for statistical analysis, drafting of the article, writing the manuscript, and final revision for publication. All authors have read and approved the manuscript.

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Availability of data and materials

Data is available with the authors on request.

Declarations

Ethics approval and consent to participate

Received approval from Research Ethics Committee of Kasr Alainy, Faculty of Medicine, Cairo University (number: I:141014); consent to participate was not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflict of interest.

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ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state

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1 | SUMMARY OF WHAT IS NEW OR DIFFERENT

Changes to previous recommendations include:

- Biochemical criteria to diagnose diabetic ketoacidosis (DKA) include serum bicarbonate <18 mmol/L
- Infusion of initial fluid bolus(es) over 20–30 min
- Promoting a rise in serum sodium concentrations during DKA treatment is no longer considered necessary
- Increased emphasis on differences in treatment recommendation for HHS and mixed presentation of DKA and HHS (hyperosmolar DKA) compared to standard DKA treatment

2 | EXECUTIVE SUMMARY

The **biochemical criteria** for the diagnosis of DKA are:

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dl])
- Venous pH <7.3 or serum bicarbonate <18 mmol/L(C)
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) (C) or moderate or large ketonuria.

Not all children or caregivers volunteer classic symptoms of diabetes (polyuria, polydipsia) at the time of diagnosis of DKA, and other symptoms of DKA are non-specific. Therefore, fingerstick blood glucose measurements should be considered for all children presenting with rapid breathing or with vomiting and abdominal pain without diarrhea.

The following recommendations are based on currently available evidence and are intended to be a general guide to DKA management. Because there is considerable individual variability in presentation of DKA (ranging from mild to severe and life threatening), some children may require specific treatment that, in the judgment of the treating physician, may occasionally be outside the range of options presented here. Clinical judgment should be used to determine optimal treatment for the individual child, and timely adjustments to treatment should be based on ongoing clinical and biochemical monitoring of the response to treatment.

Emergency assessment should follow the general guidelines for Pediatric Advanced Life Support (PALS) and includes: Immediate measurement of blood glucose, blood or urine ketones, serum electrolytes and blood gases; and assessment of level of consciousness. (E) Two peripheral intravenous (IV) catheters should be inserted (E).

Management should be conducted in a center experienced in the treatment of DKA in children and where vital signs, neurological status, and laboratory results can be monitored frequently. (E) Where geographic constraints require that management be initiated in a center with less experience, there should be telephone or videoconference support from a physician with expertise in DKA (E).

Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by clinical or laboratory data (E).

Goals of therapy are to correct dehydration, correct acidosis and reverse ketosis, gradually restore hyperosmolality and blood glucose concentration to near normal, monitor for acute complications, and identify and treat any precipitating event.

Fluid replacement should begin before starting insulin therapy. Expand volume using one or more boluses of 0.9% saline infused over 20–30 min to restore peripheral circulation (E). Calculate the subsequent rate of fluid administration (0.45% to 0.9% saline), including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit over 24 to 48 h (A).

Insulin therapy: begin with 0.05–0.1 U/kg/h (0.05 U/kg/h can be considered with pH > 7.15) at least 1 h AFTER starting fluid replacement therapy (B).

Potassium: If the child has hyperkalemia (potassium >5.5 mmol/L), *defer* potassium replacement therapy until urine output is documented. Begin intravenous fluid treatment with non-potassium containing fluids and measure potassium hourly. Begin potassium infusion when potassium <5.5 mmol/L. In the rare child with hypokalemia (potassium <3.0 mmol/L), *defer* insulin treatment and give a bolus of potassium (not to exceed 0.5 mEq/Kg/h), along with cardiac monitoring. Otherwise, begin with 40 mmol potassium/L (E).

Bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia or for severe acidosis (venous pH < 6.9) *with evidence of compromised cardiac contractility* (C).

Warning signs and symptoms of cerebral injury include: Onset of headache or vomiting after beginning treatment or progressively worsening or severe headache, slowing of heart rate not related to sleep or improved intravascular volume, change in neurological status (irritability, lethargy, confusion, incontinence), specific neurological signs (e.g., cranial nerve palsies), decreased oxygen saturation. (C) Hypertension occurs commonly in children with DKA and should not be considered a warning sign for cerebral injury, in the absence of other findings.

In children with multiple risk factors for cerebral injury (elevated serum urea nitrogen concentration (>20 mg/dl), severe acidosis (pH < 7.1), severe hypocapnia (pCO_2 < 21 mmHg), age < 5 years), have mannitol or hypertonic saline at the bedside and the dose calculated. (E) If neurologic status deteriorates acutely, hyperosmolar therapy with mannitol or hypertonic saline should be given immediately (C).

Prevention: Management of DKA is not complete until an attempt has been made to identify and treat the cause. DKA without a preceding illness in a child with known diabetes is almost always the result of failure to appropriately administer insulin injections or interruption of insulin delivery, most often as a result of insulin pump infusion set dysfunction. In new onset diabetes, DKA is frequently the consequence of a delay in diagnosis (E).

The criteria for **Hyperglycemic Hyperosmolar State (HHS)** include all the following:

- Plasma glucose concentration > 33.3 mmol/L (600 mg/dl)
- Venous pH > 7.25; arterial pH > 7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Effective serum osmolality >320 mOsm/kg

In HHS, the goals of initial fluid therapy are to expand the intra- and extravascular volume, restore normal renal perfusion, and promote a gradual decline in corrected serum sodium concentration and serum osmolality. Differences in treatment strategy between HHS and DKA include the volume of fluid administered, the timing of insulin administration, and monitoring of the decline in corrected serum sodium concentration.

In HHS, begin **insulin administration** at a dose of 0.025 to 0.05 U/kg/h once plasma glucose is decreasing less than 3 mmol/L (50 mg/dl) per hour with fluid alone (C). Rates of fluid administration, both as initial fluid boluses to restore circulation and as ongoing deficit replacement, are substantially higher than for DKA.

3 | PATHOPHYSIOLOGY

Diabetic ketoacidosis (DKA) results from deficiency of circulating insulin and increased levels of the counterregulatory hormones: glucagon, catecholamines, cortisol and growth hormone.[1–3] In most cases, DKA is caused by new onset of diabetes, omission of insulin injections, interruption of insulin delivery in children using an insulin pump, or inadequate management of an infection. Severe insulin deficiency occurs in previously undiagnosed T1D and when patients deliberately or inadvertently do not inject insulin, especially the long-acting component of a basal-bolus regimen, or markedly reduce the doses of insulin, for example, during an intercurrent illness such as gastroenteritis. Children who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason.[4] Relative insulin deficiency occurs when the concentrations of counterregulatory hormones markedly increase in conditions such as sepsis, trauma, or febrile illness, which overwhelm homeostatic mechanisms and lead to metabolic decompensation despite the patient injecting the usual recommended dose of insulin.

The combination of absolute or relative insulin deficiency and high counterregulatory hormone concentrations causes an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis) and impaired peripheral glucose utilization, which result in hyperglycemia and hyperosmolality. Insulin deficiency and high counterregulatory hormone concentrations also increase lipolysis and ketogenesis and cause ketonemia and metabolic acidosis. Hyperglycemia exceeding the usual renal threshold of approximately 10 mmol/L (180 mg/dl) together with hyperketonemia cause osmotic diuresis and obligatory loss of electrolytes (sodium, potassium, phosphate, magnesium) leading to dehydration, often aggravated by vomiting associated with severe ketosis. These changes stimulate further stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and

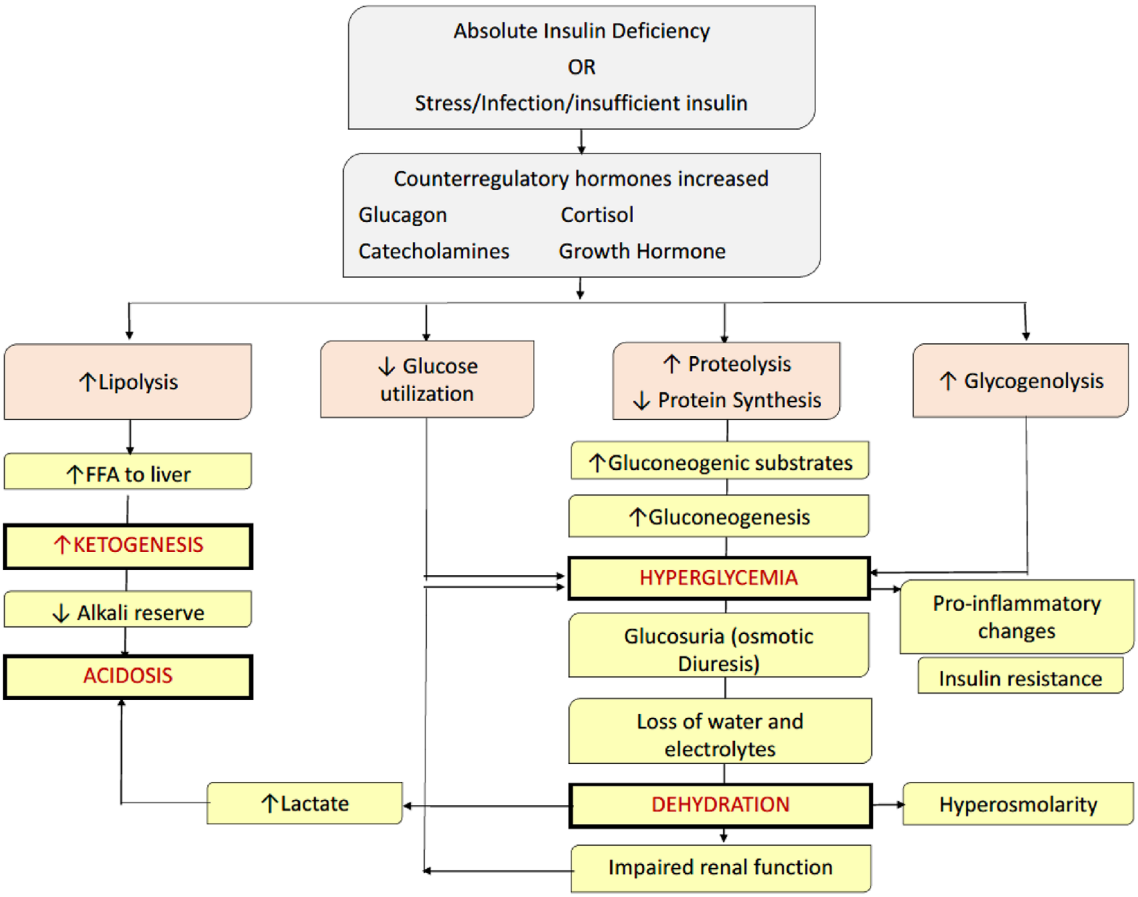

FIGURE 1 Pathophysiology of diabetic ketoacidosis. Copyright © 2006 American Diabetes Association. Adapted from diabetes care, Vol. 29, 2006:1150–1159. Reprinted with permission of *The American Diabetes Association*

hyperketonemia. Lactic acidosis from hypoperfusion may contribute to the acidosis.[5,6] Hyperglycemia also causes a hyperinflammatory state that increases insulin resistance and is involved in the pathophysiology of several DKA complications. If this cycle is not interrupted by exogenous insulin together with fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue (Figure 1).

Diabetic ketoacidosis (DKA) is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments[5]; the typical range of losses is shown in Table 1. Despite substantial dehydration, children generally continue to maintain normal blood pressure or even have high blood pressure,[7,8] possibly due to elevated plasma catecholamine concentrations, increased release of antidiuretic hormone (ADH) in response to hyperosmolality (which increases blood pressure via vasporessin 2 receptors), increased osmotic pressure from marked hyperglycemia, or other factors.[7,8] Considerable urine output persists because of glucosuria until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the specific deficits in an individual child vary depending upon the duration and severity of illness, the extent to which the child was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (fruit juices or sugar-containing soft drinks) may exacerbate hyperglycemia.[9]

Clinical manifestations of diabetic ketoacidosis

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness

4 | DEFINITION OF DIABETIC KETOACIDOSIS

The diagnosis of DKA is based on the triad of hyperglycemia, ketosis and metabolic acidosis; however, specific biochemical criteria used to

TABLE 1 Losses of fluid and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-h maintenance requirements
Water	70 ml (30–100)	* ≤ 10 kg 100 ml/kg/24 h 11–20 kg 1000 ml + 50 ml/kg/24 h for each kg from 11–20 >20 kg 1500 ml + 20 ml/kg/24 h for each kg >20
Sodium	6 mmol (5–13)	2–4 mmol[a]
Potassium	5 mmol (3–6)	2–3 mmol
Chloride	4 mmol (3–9)	2–3 mmol
Phosphate	0.5–2.5 mmol	1–2 mmol

Note: Data are from measurements in only a few children and adolescents.[124–128] In any individual patient, actual losses may be less or more than the ranges shown.
Note: Three methods for determining maintenance water requirements in children are commonly used: *the Holliday–Segar formula[273] (Table 1), a simplified Holliday-Segar formula (see below), and a formula based on body surface area for children who weigh more than 10 kg (1500 ml/m^2/24 h).[274]
Note: Simplified method based on Holliday–Segar: <10 kg 4 ml/kg/h; 11–20 kg 40 + 2 ml/kg/h for each kg between 11 and 20; >20 kg 60 + 1 ml/kg/h for each kg >20.
[a]Maintenance electrolyte requirements in children are per 100 ml of maintenance IV fluid.[274,275]

define DKA vary in different parts of the world and among different research studies.[3] All three biochemical criteria are required to diagnose DKA[10]:

- Hyperglycemia (blood glucose >11 mmol/L [200 mg/dl])
- Venous pH < 7.3 or serum bicarbonate <18 mmol/L
- Ketonemia* or ketonuria

*Although not universally available, blood beta-hydroxybutyrate (BOHB) concentration should be measured whenever possible. BOHB ≥3 mmol/L is a sensitive indicator of DKA[11] but is not as specific as a value of ≥5.3 mmol/L, which has optimal accuracy (~91%) for predicting DKA in children with hyperglycemia presenting to an Emergency Department.[12] Urine ketones are typically ≥2+ ("moderate or large"). Urine ketone testing detects acetoacetate and acetone but not BOHB, the main ketone in DKA.[13] Therefore, reliance on urine testing alone may underestimate the severity of ketonemia. Several sulfhydryl-containing drugs (captopril, N-acetylcysteine, mesna, penicillamine) and valproic acid, which is partly eliminated as a ketone-containing metabolite,[14] give false positive urine tests.[15,16] Expired or improperly stored urine test strips can give false negative results.[17]

Partially treated children and those who have consumed little or no carbohydrate may have only modestly elevated blood glucose concentrations, referred to as euglycemic ketoacidosis.[18,19] This can be caused by starvation/fasting, a low carbohydrate-high fat diet, or the off-label use of SGLT2-inhibitors.[20–23] Management of euglycemic ketoacidosis should follow standard DKA guidelines except that dextrose-containing fluids should be started earlier, immediately after initial volume expansion. Serum bicarbonate concentration alone can substitute for venous pH to diagnose DKA and classify severity in children with new onset diabetes mellitus and is an alternative to venous pH in circumstances where pH measurement is not available.[24]

The frequency of type 2 diabetes in the pediatric age range is increasing worldwide.[25–28] Overall, 5% to 25% of children with type 2 diabetes have DKA at the time of diagnosis.[29,30] In the SEARCH for Diabetes in Youth Study in the USA, DKA occurred in nearly 6% of youth with type 2 diabetes.[31,32]

The **severity of DKA** is categorized by the degree of acidosis[10,33]

- Mild: venous pH < 7.3 or serum bicarbonate <18 mmol/L[24]
- Moderate: pH < 7.2 or serum bicarbonate <10 mmol/L
- Severe: pH < 7.1 or serum bicarbonate <5 mmol/L

Diabetic ketoacidosis (DKA) should be distinguished from HHS, which is characterized by severe hyperglycemia and markedly increased serum osmolality without substantial ketosis and acidosis. HHS may occur in children with type 2 diabetes,[30,34–36] type 1 diabetes,[37] cystic fibrosis,[35] and in infants, especially those with neonatal diabetes.[38,39] Medications such as corticosteroids[40] and atypical antipsychotics[41] can precipitate HHS. Although definitions vary slightly,[3] a committee of the Pediatric Endocrine Society proposed the following **criteria for HHS** in the pediatric age range[42]:

- plasma glucose concentration >33.3 mmol/L (600 mg/dl)
- arterial pH > 7.30; venous pH > 7.25
- serum bicarbonate >15 mmol/L
- small ketonuria, absent to small ketonemia*
- effective serum osmolality >320 mOsm/kg
- obtundation, combativeness, or seizures (in approximately 50%)

The characteristic features of HHS and DKA may overlap and some children with HHS, especially those with severe dehydration, may have mild or moderate acidosis that is mainly due to hypoperfusion and lactic acidosis. Conversely, some children with DKA may have features of HHS (severe hyperglycemia).[9] Therapy must be appropriately modified to address the pathophysiology and particular biochemical disturbances of the individual child (see below).

5 | FREQUENCY AND CAUSES OF DKA

Children with new onset of type 1 diabetes (T1D) frequently present with DKA. Frequencies range from approximately 15% to 70% in Europe and North America.[32,43–51] Several countries have reported recent increases in the frequency of DKA at diagnosis of T1D.[51–53] Very young children and those of underserved ethnic groups are at increased risk of presenting with DKA.[54,55] Delayed diagnosis of diabetes is an important factor increasing the risk of DKA and this association has been particularly evident during the SARS-CoV2 pandemic.[56–59] Prevention campaigns targeting awareness of diabetes

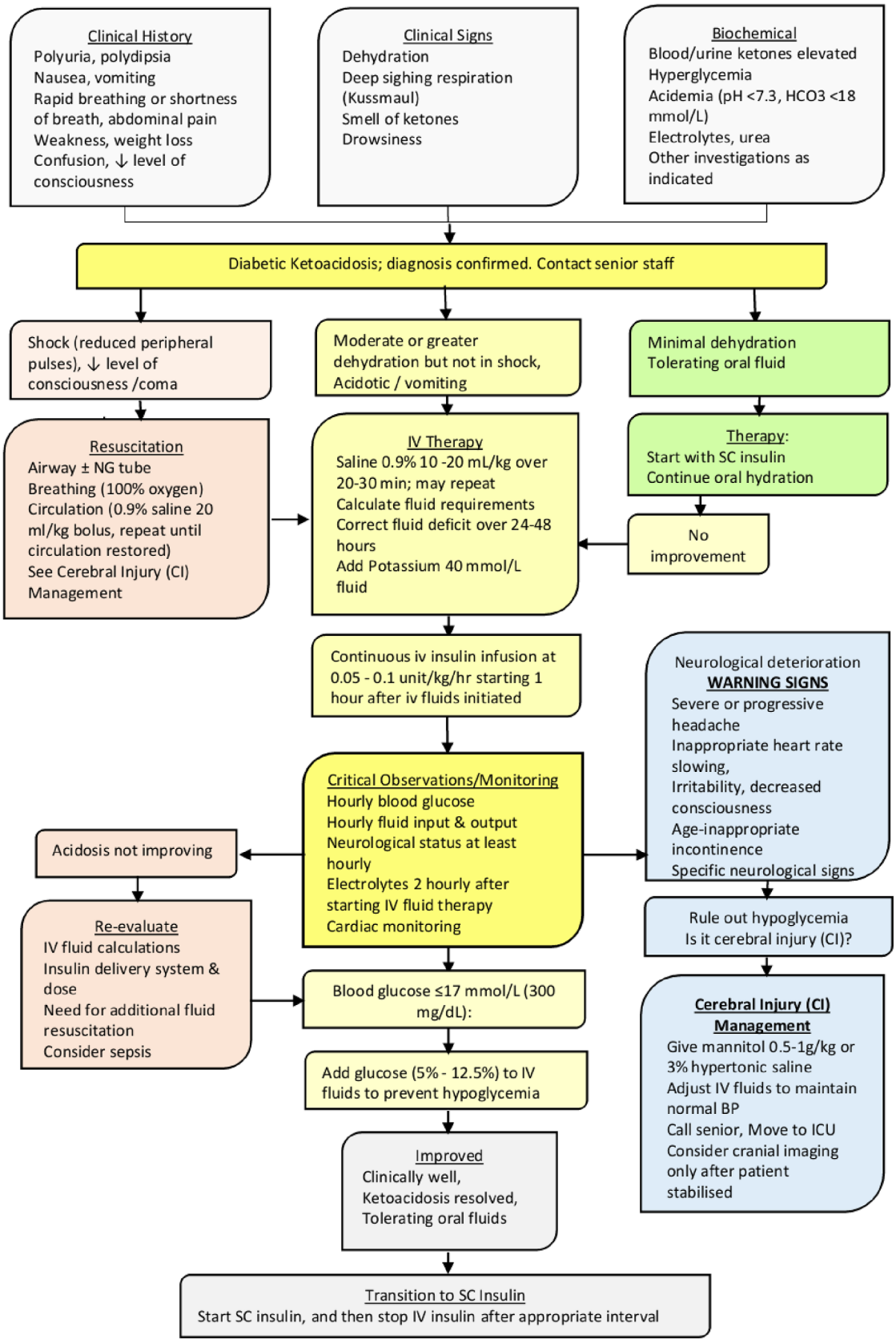

FIGURE 2 Algorithm for the management of DKA. Adapted from Pinhas-Hamiel and Sperling.[272] NG, nasogastric; SC, subcutaneous.

TABLE 2 Glasgow coma scale (GCS)

Best eye response	Best verbal response	Best verbal response (nonverbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent[a]	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation[b]	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Oriented, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain
			6. Obeys commands

Note: The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best.[81] One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.
[a]Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.
[b]Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

symptoms have been successful in reducing DKA frequency.[60] In children with established diabetes, the risk of recurrent DKA is 1%–10% per patient-year.[4,61–66] Most cases of DKA in children with established diabetes are due to insulin omission or interruption of insulin delivery in children using insulin pumps.[63,64] A minority of DKA cases in children are caused by infections (mainly gastroenteritis).

6 | MANAGEMENT OF DKA

6.1 | Emergency assessment

Acute management (Figure 2) should follow the general guidelines for PALS,[67,68] with particular attention to the following:

- Obtain vital signs and measure weight–The current weight should be used for calculations and not a weight from a previous visit. If body surface area is used for fluid therapy calculations, measure height or length to determine surface area. Note that despite severe dehydration, hypertension occurs in 12% of children with DKA at presentation and develops during treatment in an additional 16%.[7]
- Insert peripheral intravenous line, obtain blood for laboratory evaluation, and start intravenous fluid therapy following guidelines (see Section 6.3).
- Immediately measure blood glucose and blood BOHB levels with bedside meters or urine acetoacetic acid concentrations with urine test strips if bedside blood ketone measurements are not available. Measurement of blood BOHB concentration with a point-of-care meter, if available, is very useful to confirm ketoacidosis (≥3 mmol/L in children)[11] and to monitor the response to treatment.[12,69–75]
- Measure venous pH, pCO_2, glucose, electrolytes (including serum bicarbonate), serum urea nitrogen, and creatinine.
- Perform a detailed history and physical exam with particular attention to mental status and any possible source of infection.
- **Severity of dehydration**
  - Estimation of the degree of dehydration is imprecise in DKA and shows only fair to moderate agreement among examiners.[76–78] The most useful clinical signs for predicting dehydration are:
    - prolonged capillary refill time (normal capillary refill is ≤2 s), abnormal skin turgor ('tenting' or inelastic skin), dry mucus membranes, sunken eyes, absent tears, weak pulses, cool extremities.[79]
  - Laboratory measures have been found to be better predictors of dehydration severity than clinical signs.[80] These include:
    - Higher serum urea nitrogen (>20 mg/dl)
    - Lower pH (<7.1)
  - ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension or oliguria.
- **Assess level of consciousness** (Glasgow coma scale [GCS]–see Table 2)[81,82]
- In the unconscious or severely obtunded child **without normal airway protective reflexes**, **secure the airway** by rapid sequence intubation.
  - Insert a nasogastric tube with continuous suction to prevent pulmonary aspiration.
  - Intubation should be avoided if possible; an increase of pCO_2 during or following intubation above the level that the patient had been maintaining may cause cerebrospinal fluid (CSF) pH to decrease and contribute to worsening of cerebral injury.[83,84]
- Give **oxygen** to patients with circulatory impairment or shock.
- A continuous **cardiac monitor** should be used to assess degree of tachycardia, monitor for arrhythmias, and assess T-waves for evidence of hyper- or hypokalemia.[85,86]
- A second **peripheral intravenous (IV) catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may, rarely, be necessary in some critically ill children managed in an intensive care unit.
  - Unless absolutely necessary, **avoid placing a central venous catheter** because of the high risk of thrombosis. If a central catheter has been inserted, the catheter should be removed as soon as the child's clinical status permits.[87,88] Mechanical and pharmacologic prophylaxis (low molecular weight heparin) should be considered for those with central venous catheters, especially in children >12 years.

- Insulin should not be given through a central line unless it is the only available option because its infusion may be interrupted when other fluids are given through the same line.
- **Antibiotics** may be required for **children with evidence of infection** after obtaining appropriate cultures such as blood, urine, spinal fluid, throat, or tracheal aspirate as indicated.
- Bladder catheterization usually is not necessary but should be considered if the child is unconscious or severely ill.
- **Additional laboratory measurements** include:
  - Hemoglobin/ hematocrit
  - Albumin, calcium, phosphate and magnesium concentrations
  - Hemoglobin A1c may be useful to confirm the diagnosis of diabetes (e.g., in a child with hyperglycemia suspected to be due to a stress response and metabolic acidosis caused by dehydration) or as an indicator of duration of hyperglycemia
  - Complete blood counts (CBC) frequently show increased WBC and left shift in children with DKA, even without infection. Infection evaluation should be based on the clinical scenario and not on the white cell count.
- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram** (ECG) for baseline evaluation of potassium status.[85,86]

6.2 | Where should the child with DKA be managed?

After initial life support, the child should receive care in a unit that has:

- Experienced nursing and medical staff trained in pediatric DKA management who are available to perform meticulous monitoring until DKA has resolved.
- Care policies and procedures based on clinical practice guidelines. Staff should have access to clinical practice guidelines in written or electronic format.
- Access to a laboratory that can provide frequent and timely measurements of biochemical variables.

Whenever possible, a specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management. If this is not possible due to geographic or resource constraints, arrangements should be made to access telephone or videoconference support from a physician with expertise in DKA management.

Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral injury (e.g., <5 years of age, pH < 7.1, pCO_2 < 21 mmHg, blood urea nitrogen > 20 mg/dl) should be considered for immediate treatment in an intensive care unit (pediatric if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care. Transport teams should be knowledgeable about DKA management or have access to a medical control physician with appropriate expertise and have rescue medications available during transport, including high concentration IV dextrose solutions and mannitol or 3% hypertonic saline.

In a child with **established diabetes**, whose parents have been trained in sick day management, hyperglycemia, and ketosis without vomiting or severe dehydration can be managed at home with subcutaneous insulin, or in an outpatient health care facility (e.g., emergency ward) with supervision from an experienced diabetes team.[33,89,90]

Goals of therapy

- Correct acidosis and reverse ketosis
- Correct dehydration
- Restore blood glucose to near normal
- Monitor for complications of DKA and its treatment
- Identify and treat any precipitating event

6.3 | Fluid and electrolyte replacement

6.3.1 | Principles of fluid and electrolyte therapy

Children with DKA have a deficit in extracellular fluid (ECF) volume that is typically about 7% of body weight.[76,78,80] Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit based on physical exam and vital signs are inaccurate[76,78,80]; therefore, in mild DKA assume 5%, moderate DKA 7% and severe DKA 10% dehydration. Increased serum urea nitrogen and anion gap at presentation are the measures most strongly correlated with volume deficit.[80] The serum sodium concentration is an unreliable measure of the degree of ECF contraction because glucose largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia.[91] It is useful to calculate the corrected sodium concentration to help assess relative deficits of sodium and water (the formula for corrected sodium can be found in the Monitoring section).[5,92] The "corrected" sodium represents the expected serum sodium concentration in the absence of hyperglycemia. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase and the glucose-corrected sodium concentration should slowly decrease or remain in the normal range.

The objectives of fluid and electrolyte replacement therapy are to:

- Restore circulating volume

- Replace sodium and water deficits
- Improve glomerular filtration and enhance clearance of glucose and ketones from the blood

Controversies surrounding optimal fluid treatment regimens for children with DKA have largely focused on the role of intravenous fluids in causing or contributing to risk of cerebral edema and cerebral injury.[93–95] Although the pathogenesis of DKA-related cerebral injury remains incompletely understood, recent evidence suggests that abnormalities in cerebral perfusion and the hyperinflammatory state caused by DKA play important roles, and that variations in fluid treatment likely have minimal effects.[95–99] A large prospective randomized clinical trial (the PECARN FLUID Trial) compared acute and long-term neurological outcomes in 1389 children with DKA treated with slower versus more rapid fluid administration using either 0.45% saline or 0.9% saline.[96] The PECARN FLUID Trial showed no significant differences in the frequency of either altered mental status or clinical diagnoses of cerebral injury in any of the treatment arms, and long-term neurocognitive outcomes were similar in all groups. Point estimates suggested lower frequencies of altered mental status in children rehydrated more rapidly with 0.45% saline, but these differences did not reach statistical significance.[96] The results of this study suggest that a range of fluid protocols can be safely used to treat DKA in children, and that clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion. As protocols outside of the range used in the PECARN FLUID Trial have not been thoroughly investigated, we recommend that fluid treatment remain within the variations used in the trial. These include assumed fluid deficits between 5% and 10% of body weight, replacement of deficits over 24 to 48 h,† provision of maintenance fluids, and use of fluids with a sodium content between 0.45% and 0.9% NaCl. Although previous retrospective studies have found associations between declines in serum sodium concentrations during DKA treatment and DKA-related cerebral injury,[100,101] a recent large prospective study found no such association.[102] In that study, declines in glucose-corrected sodium concentrations were not associated with altered mental status or clinically apparent cerebral injury. Serum sodium trends during DKA treatment largely reflected the balance of sodium and water losses at presentation, with those presenting with higher initial sodium concentrations (greater free water losses) normalizing sodium concentrations during treatment. The study also found that the sodium content of intravenous fluids significantly influenced changes in sodium concentrations during treatment, but the rate of infusion of intravenous fluids had minimal effects. These findings suggest that promoting a rise in the serum sodium concentration need not be a routine focus of DKA treatment. In the event that changes in serum sodium concentration are required, the sodium content of intravenous fluids should be adjusted, but not the rate of infusion.

The principles described below are based on consensus statements from panels of expert physicians representing the Pediatric Endocrine Society (PES), the European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD)[10,103–105] and incorporate the recommendations from the PECARN FLUID Trial[96] and other recent data. Note that IV fluids given in another facility before assessment should be factored into calculations of deficit and replacement volumes.

6.3.2 | Resuscitation fluids

For children who are volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline, 10 to 20 ml/kg infused over 20–30 min to restore the peripheral circulation. If tissue perfusion is poor the initial fluid bolus volume should be 20 ml/kg.

- In the rare child with DKA in shock, rapidly restore circulatory volume with 0.9% saline in 20 ml/kg boluses infused as quickly as possible through a large bore cannula with reassessment of circulatory status after each bolus.
- Use crystalloid not colloid. There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.

6.3.3 | Deficit replacement fluids

Subsequent fluid management (deficit replacement) can be accomplished with 0.45%–0.9% saline or a balanced salt solution (Ringer's lactate, Hartmann's solution or Plasmalyte).[96,100,102,106–114]

- Fluid therapy should begin with deficit replacement plus maintenance fluid requirements.
  - All children will experience a decrease in vascular volume when plasma glucose concentrations fall during treatment; therefore, it is essential to ensure that they receive sufficient intravenous fluid to maintain adequate tissue perfusion.
- Deficit replacement should be with a solution that has a tonicity in the range of 0.45%–0.9% saline, with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement).[96,100,102,106–108,110,113,115,116] Decisions regarding use of isotonic versus hypotonic solution for deficit replacement should depend on clinician judgment based on the child's hydration status, serum sodium concentration, and osmolality.
- In addition to providing the usual daily maintenance fluid requirement, replace the estimated fluid deficit (minus initial fluid bolus amount) over 24–48 h.[96] Although rehydration is generally planned to occur over 24 h or longer, DKA typically resolves before 24 h and remaining fluid deficits are replaced by oral intake after transition to subcutaneous insulin.
- Clinical assessment of circulatory status, fluid balance, and trends in serum sodium levels are valuable guides to fluid and electrolyte therapy. The serum sodium concentration typically increases as the serum glucose concentration decreases.
- Avoiding declines in intravascular volume is of particular importance for children with severe dehydration or circulatory

compromise. In these situations, the sodium content of the fluid should be increased if the measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls.[102,112]

- Urinary losses should not routinely be added to the calculation of replacement fluid, but this may be necessary in some circumstances, particularly in children with a mixed presentation of DKA and HHS (see below). Careful monitoring of fluid intake and output is essential to ensure positive fluid balance.
- Calculation of fluid infusion rates for obese children should be similar to those of other children. Using ideal body weight for fluid calculations for these children is not necessary. If fluid calculations for obese children exceed those typically used in adult protocols, then adult DKA fluid protocols can be used (e.g., 1 L maximum per bolus and 500 ml/h fluid infusion).
- The use of large amounts of chloride-rich fluids (combined with preferential renal excretion of ketones over chloride) is often associated with development of hyperchloremic metabolic acidosis.[116–121]
  - When hyperchloremia develops, a persisting base deficit or low bicarbonate concentration can be erroneously interpreted as being due to ongoing ketosis.[122]
  - To avoid this misinterpretation, measurement of bedside BOHB levels (or calculation of anion gap if bedside BOHB is not available) should be used to determine resolution of ketoacidosis.
  - Hyperchloremic acidosis is generally asymptomatic and resolves spontaneously.
  - The chloride load can be reduced by using potassium salts other than potassium chloride, or by using fluids such Ringer's lactate or Plasmalyte in which a portion of the chloride is replaced by lactate or acetate, respectively.[123]

6.3.4 | Potassium replacement

Children with DKA have total body potassium deficits on the order of 3 to 6 mmol/kg.[124–128] The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells) and acidosis, as well as glycogenolysis and proteolysis secondary to insulin deficiency.[5] Potassium is lost from the body via vomiting and osmotic diuresis. In addition, volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. The incidence and severity of hypokalemia (potassium < 3.5 mmol/L) may be higher in malnourished children.[129] In spite of total body depletion, serum potassium levels may be normal, increased, or decreased at presentation.[130] Renal dysfunction caused by DKA enhances hyperglycemia and reduces potassium excretion, thereby raising serum potassium concentrations at presentation.[130] Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum potassium levels during DKA treatment.[131] Insulin also has an aldosterone-like effect leading to increased urinary potassium excretion. High doses administered intravenously for a prolonged period may contribute to hypokalemia despite potassium administration. The duration and dosage of intravenous insulin should be minimized to decrease the risk of hypokalemia. The serum potassium concentration may decrease rapidly during treatment, predisposing to cardiac arrhythmias. Severe hypokalemia (<2.5 mmol/L) is an independent marker of poor treatment outcome and mortality.[132,133]

Potassium replacement is required regardless of the serum potassium concentration, except if renal failure is present.[125,134]

- If the child is hypokalemic, start potassium replacement *at the time of* initial volume expansion and before starting insulin therapy. For rare children with initial potassium levels <3.5 mmol/L, *defer* insulin treatment and give a bolus of potassium (not to exceed 0.5 mmol/Kg/h), along with cardiac monitoring.[135] Otherwise, start-replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the child is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. Begin infusion with non-potassium fluids, remeasure potassium hourly, and begin potassium infusion when serum potassium is below 5.5 mmol/L.
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia.[85,86] Prolongation of the PR interval, T wave flattening and inversion, ST depression, prominent U waves, apparent long QT interval (due to fusion of the T and U waves) indicates hypokalemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L.[136] Subsequent potassium replacement therapy should be based on serum potassium measurements.
- If there is hypokalemia, potassium replacement should begin concurrent with initial volume expansion, using a separate IV infusion.
- Potassium phosphate may be used together with potassium chloride or acetate; for example, 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate. Administration of potassium entirely as potassium chloride contributes to the risk of hyperchloremic metabolic acidosis, whereas administration entirely as potassium phosphate can result in hypocalcemia.
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/h.
- If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

6.3.5 | Phosphate

Phosphate depletion occurs in DKA due to osmotic diuresis and a shift of intracellular phosphate to the extracellular compartment as a result of metabolic acidosis.[5,124–126,137,138] Plasma phosphate levels

decrease during treatment due to dilution by fluid replacement and insulin-mediated entry of phosphate into cells.[137,139–141] During treatment, 50%–60% of children develop hypophosphatemia.[96] The degree of metabolic acidosis is a main determinant.[138] Although severe hypophosphatemia can occur at any time during DKA treatment, continuation of intravenous therapy without food consumption beyond 24 h is a risk factor for clinically significant hypophosphatemia.[124–126] To date, studies of phosphate replacement in children with DKA have involved small numbers of children with limited statistical power, therefore data for evidence-based guidelines is lacking.

- Severe hypophosphatemia is uncommon but can have serious consequences. Clinical manifestations are largely due to intracellular phosphate depletion. Decreased intracellular adenosine triphosphate (ATP) levels impair cellular functions that depend on energy-rich phosphate compounds, and a decrease in 2,3-diphosphoglycerate (DPG) level increases the affinity of hemoglobin for oxygen and reduces oxygen release in tissues.[142] Many organ systems can be affected. Manifestations of severe hypophosphatemia include metabolic encephalopathy, seizures,[143] impaired myocardial contractility, ventricular arrhythmia,[144] respiratory failure,[137] hemolytic anemia,[145] muscle dysfunction with proximal myopathy, dysphagia, ileus, and rhabdomyolysis.[146–149]
- Severe hypophosphatemia (<1 mg/dl [0.32 mmol/L]) with or without associated symptoms should be treated promptly.[143,150] Insulin infusion may need to be reduced or temporarily halted until phosphorus levels increase.
- Routine phosphate replacement to prevent hypophosphatemia is advisable in locations where this treatment is readily available, particularly for children with severe DKA.
- Potassium phosphate can be combined with potassium chloride or potassium acetate to provide phosphate replacement without substantial risk of hypocalcemia.
- Carefully monitor serum calcium and magnesium concentrations during phosphate infusion to avoid hypocalcemia.[151,152]

6.4 | Insulin therapy

Diabetic ketoacidosis (DKA) is caused by a decrease in the effective circulating insulin level associated with increases in counter-regulatory hormone concentrations. Although rehydration alone frequently causes a marked decrease in blood glucose concentration,[153,154] insulin therapy is essential to restore normal cellular metabolism, to suppress lipolysis and ketogenesis, and to normalize blood glucose concentrations.[155]

- Start insulin infusion 1 h after initiation of IV fluid treatment.[156]
- Correction of insulin deficiency
  - Dose: 0.05–0.1 U/kg/h of regular (soluble) insulin (e.g., one method is to dilute 50 units regular [soluble] insulin in 50 ml 0.9% saline, 1 unit = 1 ml).[157–164] The lower dosage (0.05 U/kg/h) can be considered for children with pH > 7.15.
  - Route of administration: Intravenous (IV)
  - An IV insulin bolus should *not* be used at the start of therapy; it is unnecessary,[163,165] can precipitate shock by rapidly decreasing osmotic pressure, and can exacerbate hypokalemia.
- Infusion tubing should be flushed with the insulin solution before administration.
  - If IV cannulation is not possible due to severe dehydration, insulin can be administered IM.
  - Central venous catheters should not be used for insulin administration because the large dead space may cause erratic insulin delivery.
- The dose of insulin should usually remain at 0.05–0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, serum bicarbonate >18 mmol/L, BOHB <1 mmol/L, or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations.[166] Monitor venous pH (and serum BOHB concentration where possible) every 2 h to ensure steady improvement. If the insulin effect is adequate, serum BOHB should decrease by approximately 0.5 mmol/L per hour.[70] Increase the insulin dose if the expected rate of biochemical improvement does not occur.
- If the child shows marked sensitivity to insulin (e.g., some young children with DKA, children with HHS, and some older children with established diabetes), the insulin dose may be decreased, provided that metabolic acidosis continues to resolve.
- For less severe DKA (pH > 7.15), 0.05 U/kg/h (0.03 U/kg/h for age < 5 years with mild DKA) is usually sufficient to resolve the acidosis. Uncontrolled retrospective studies and small RCTs have reported comparable efficacy and safety using 0.05 unit/kg/h compared to 0.1 unit/kg/h,[113,167–169] and some pediatric centers routinely use this dose for treatment of DKA.
- During initial volume expansion, the plasma glucose concentration falls steeply.[153] Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L per hour.[157–160,163,170]
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% dextrose should be added to the IV fluid when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dl), or sooner if the rate of fall is precipitous (>5 mmol/L/h after initial fluid expansion).
  - It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.
- If biochemical parameters of DKA (venous pH, anion gap, BOHB concentration) do not improve, reassess the child, review insulin therapy, and consider other possible causes of impaired response to insulin; for example, infection, errors in insulin preparation or route of administration.
- In circumstances where continuous IV administration is not possible and in children with uncomplicated mild to moderate DKA, hourly or 2-hourly subcutaneous (SC) rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion.[170–174] This method should not be used in children whose peripheral circulation is impaired. Dose SC:

0.15 units/kg every 2 h (initiated 1 h after the start of fluid replacement). The dose can be reduced to 0.1 unit/kg every 2 h if BG continues to decrease by >5 mmol/L (90 mg/dl) even after adding dextrose.[175–177]

- Subcutaneous administration of short-acting (regular) insulin every 4 h is another alternative in mild DKA when IV infusion or rapid-acting insulin analogs are not available.[178] A suggested starting dose is 0.13–0.17 units/kg/dose of regular insulin every 4 h (0.8–1 unit/kg/day in divided doses). Doses are increased or decreased by 10%–20% based on the blood glucose level before the next insulin injection.[178] Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving.

6.5 | Acidosis

Fluid and insulin replacement reverses acidosis. Insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids. A recent large study of children with DKA showed that faster compared to slower fluid administration caused earlier normalization of the anion gap; however, pH did not normalize more rapidly with more rapid fluid infusion, likely due to increased frequency of hyperchloremic acidosis.[117]

Lack of resolution of acidosis is most frequently due to development of hyperchloremic acidosis. This is generally a benign condition and should not delay transition to subcutaneous insulin. Rare causes of persistent acidosis include insufficient fluid administration, infection/sepsis and incorrect preparation of the intravenous insulin infusion.

Controlled trials have shown no clinical benefit from bicarbonate administration.[179–182] Bicarbonate therapy may cause paradoxical CNS acidosis[183,184] and rapid correction of acidosis with bicarbonate causes hypokalemia.[183,185,186] Bicarbonate administration may be beneficial in rare children with life-threatening hyperkalemia or unusually severe acidosis (venous pH < 6.9) that have compromised cardiac contractility.[187]

6.6 | Introduction of oral fluids and transition to SC insulin injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present).
  - Measurement of urine ketones with test strips is based on the nitroprusside reaction, which measures acetoacetate and acetone. Persistent ketonuria characteristically occurs for several hours after serum BOHB levels have returned to normal.[70,71]
  - Absence of ketonuria should *not* be used as an endpoint for determining resolution of DKA.
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, a dose of basal (long-acting) insulin should be administered in addition to rapid- or short-acting insulin. The most convenient time to change to SC insulin is just before a mealtime. Alternatively, basal insulin may be given while the child is still receiving intravenous insulin infusion. This method is safe and may help to facilitate transition to a subcutaneous regimen.[188,189]
- To prevent rebound hyperglycemia, the first SC injection should be given 15–30 min (with rapid-acting insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With long-acting insulin, the overlap should be longer, and the rate of IV insulin administration gradually decreased. For example, for children on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the IV insulin infusion is stopped the next morning.
- The regimen, dose, and type of SC insulin should be according to local preferences and circumstances.
- After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia.

7 | CLINICAL AND BIOCHEMICAL MONITORING

Successful management of DKA and HHS requires **meticulous monitoring** and recording of the clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by clinical or laboratory data. There should be documentation on a **flow chart** of hour-by-hour clinical observations, medications, fluids, and laboratory test results.

Monitoring during the initial treatment of DKA should include the following:

- **Hourly (or more frequently as indicated)**
  - **Vital signs** (heart rate, respiratory rate, blood pressure)
  - **Neurological assessment** (Glasgow coma scale score or similar assessments; Table 2) for warning signs and symptoms of cerebral injury (see Section 8.2)
  - Amount of administered insulin
  - Accurate **fluid input** (including all oral fluid) **and output**.
  - **Capillary blood glucose** concentration should be measured hourly (but must be crosschecked against laboratory venous glucose because capillary methods may be inaccurate when there is poor peripheral circulation and when plasma glucose levels are extremely high). The utility of continuous monitoring of interstitial glucose during DKA management is currently being evaluated.[190]
- **At admission and every 2–4 h,** or more frequently, as clinically indicated
  - Serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphate, and blood gases
  - Blood BOHB concentrations, if available, are useful for tracking DKA resolution.[11,12,69–71,73,75] Point-of-care BOHB measurements correlate well with a reference method up to 3 mmol/L, but are not accurate above 5 mmol/L.[73,191]

- Laboratory observations
  - Serum may be lipemic, which in extreme cases can interfere with accuracy of electrolyte measurements in some laboratories.[192]
  - If the laboratory cannot provide timely results, a portable biochemical analyzer that measures serum electrolytes and blood gases on finger stick blood samples at the bedside is a useful adjunct to laboratory-based determinations. Blood glucose and blood or urine ketone concentrations can also be measured at the bedside while awaiting results from the laboratory.
- Measure body weight each morning
- **Calculations**:
  - Anion gap = Na − (Cl + HCO_3): normal is 12 ± 2 mmol/L
    - In DKA the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis[193,194]
  - Corrected sodium = measured Na + 1.6([plasma glucose − 5.6]/5.6) mmol/L or measured Na + 1.6([plasma glucose − 100]/100) mg/dL[91,92,195]
  - Effective osmolality (mOsm/kg) = 2 × (plasma Na) + plasma glucose mmol/L; normal range is 275–295 mOsm/kg

8 | COMPLICATIONS

8.1 | Morbidity and mortality

Diabetic ketoacidosis (DKA) is associated with a wide range of complications. These include:

- **Mortality** mainly due to cerebral injury. In developed countries, the death rate from DKA is <1%, while in developing countries it is much higher reaching 3%–13%.[196–199] The mortality rate in HHS is reported to be higher; however, reliable data are lacking in pediatric populations.
- **Permanent severe neurological sequelae** resulting from DKA-related brain injuries are infrequent. However, alterations in memory, attention, verbal intelligence quotient, and brain microstructure may result from apparently uncomplicated DKA episodes. Even a single DKA episode is associated with subtle memory declines soon after a T1D diagnosis.[200,201]
- **Renal tubular damage (RTD) and acute kidney injury (AKI)**[202–204] occurs in a high proportion (43% to 64%) of children hospitalized for DKA and is more common among children with more severe acidosis and volume depletion.[203,204] AKI is defined by the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria (AKI Stage 1, 2, or 3 defined by serum creatinine 1.5, 2, or 3 times estimated baseline creatinine).[205] RTD and AKI are managed with the restoration of fluid, electrolyte and glycemic balance.

Other complications include:

- Hypokalemia*
- Hypoglycemia
- Hypocalcemia, hypomagnesemia[151]
- Severe hypophosphatemia[138,143,145,149] *
- Hyperchloremic acidosis[117]
- Hypochloremic alkalosis[206]
- Other central nervous system complications including cerebral venous sinus thrombosis, basilar artery thrombosis, intracranial hemorrhage, cerebral infarction[207–209]
- Deep venous thrombosis[87,88,210] *
- Pulmonary embolism[211] *
- Rhinocerebral or pulmonary mucormycosis[212,213]
- Aspiration pneumonia*
- Pulmonary edema[214,215] *
- Adult respiratory distress syndrome (ARDS)[216]
- Prolonged QTc[217,218]
- Pneumothorax, pneumomediastinum and subcutaneous emphysema[219,220]
- Rhabdomyolysis[221] *
- Ischemic bowel necrosis[222]
- Renal failure*
- Acute pancreatitis[223] *

*These complications, often with fatality, have been more frequent in HHS.[224] The pathophysiology and management of HHS are discussed in the other sections of this guideline.

8.2 | Cerebral injury

The incidence of clinically overt DKA-related cerebral injury is 0.5%–0.9% and the mortality rate is 21%–24%.[101,225,226] Mental status abnormalities (GCS scores <14) occur in approximately 4%–15% of children treated for DKA and are often associated with mild cerebral edema on neuroimaging.[227,228] Neuroimaging studies have led to the appreciation that cerebral edema is not a rare phenomenon in children with DKA but occurs frequently and with varying severity.[227,229,230] Clinically overt cerebral injury represents the most severe manifestation of a common phenomenon.[231]

The cause of DKA-related cerebral injury is a topic of ongoing investigation. Rapid fluid administration resulting in changes in serum osmolality was initially thought to be the cause, however, more recent evidence suggests that cerebral hypoperfusion and the hyperinflammatory state caused by DKA play central roles.[98,232–236] It is noteworthy that the degree of cerebral edema that develops during DKA correlates with the degree of dehydration and hyperventilation at presentation, but not with initial osmolality or osmotic changes during treatment.[228] Evidence of neuroinflammation has been demonstrated in animal models of DKA, including elevated cytokine and chemokine concentrations in brain tissue, activation of brain microglia and reactive astrogliosis.[98,99,237–240] Disruption of the blood–brain-barrier has also been found in DKA, particularly in cases of fatal cerebral injury.[236,241,242]

Cerebral injury occurs more frequently in younger children,[243] those with new onset of diabetes,[198,243] and those with longer

duration of symptoms.[244] These risk associations may reflect the greater likelihood of severe DKA in these children. Epidemiological studies have identified several biochemical risk factors at diagnosis including:

- Greater hypocapnia at presentation after adjusting for degree of acidosis[101,228,245]
- Increased serum urea nitrogen at presentation[101,228]
- More severe acidosis at presentation[156,246,247]

Bicarbonate treatment for correction of acidosis has also been associated with increased risk of cerebral injury. This association was found to persist after adjusting for DKA severity.[101,248]

Clinically significant cerebral injury usually develops within the first 12 h after treatment has started but can occur before treatment has begun[101,225,249–251] or, rarely, may develop as late as 24–48 h after the start of treatment.[101,243,252] Symptoms and signs are variable. Mild to moderate headache at presentation is not unusual in children with DKA, however, development of headache or substantial worsening of headache after commencing treatment is concerning. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below.[253] One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%. Signs that occur before treatment should not be considered in the diagnosis. Neuroimaging is not required for diagnosis of cerebral injury.

Diagnostic criteria

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

Major criteria

- Altered mentation, confusion, fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure > 90 mmHg
- Age <5 years

8.2.1 | Treatment of cerebral injury

- Initiate treatment as soon as the condition is suspected.
- Adjust fluid administration rate as needed to maintain normal blood pressure while avoiding excessive fluid administration that might increase cerebral edema formation. Assiduously avoid hypotension that might compromise cerebral perfusion pressure.
- Hyperosmolar agents should be readily available at the bedside.
- Give mannitol, 0.5–1 g/kg IV over 10–15 min.[254–256] The effect of mannitol should be apparent after ~15 min and is expected to last about 120 min. If necessary, the dose can be repeated after 30 min.
- Hypertonic saline (3%), suggested dose 2.5–5 ml/kg over 10–15 min, may be used as an alternative to mannitol, or in addition to mannitol if there has been no response to mannitol within 15–30 min.[257,258]
  - 3% Hypertonic saline 2.5 ml/kg is equimolar to mannitol 0.5 g/kg. Intubation may be necessary for the patient with impending respiratory failure due to severe neurologic compromise. For intubated patients, the PCO_2 level should approximate that predicted for the level of metabolic acidosis. Hypocapnia beyond this level should be avoided except when necessary to treat clinically overt elevated intracranial pressure.[259]
- *After* hyperosmolar treatment has been started, cranial imaging may be considered. However, treatment of the clinically symptomatic patient should not be delayed in order to obtain imaging.[260] The primary concern that would warrant neuroimaging is whether the patient has a lesion requiring emergency neurosurgery (e.g., intracranial hemorrhage) or a lesion that may necessitate anticoagulation (e.g., cerebrovascular thrombosis), as suggested by clinical findings, particularly focal neurologic deficits.[207,261,262]

9 | PREVENTION OF RECURRENT DKA

Most episodes of DKA in children with previously diagnosed diabetes are the result of insulin omission, either inadvertent or deliberate. Families of children with recurrent episodes of DKA should work with a diabetes professional to ensure proper understanding of procedures for managing sick days and insulin pump failures. A social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to DKA episodes when deliberate insulin omission is suspected.

10 | HYPERGLYCEMIC HYPEROSMOLAR STATE

This syndrome is characterized by extremely elevated serum glucose concentrations and hyperosmolality without significant ketosis. Rates of treatment complications and mortality are substantially higher than those of DKA.[42] The incidence of HHS in children and adolescents is increasing[35] with up to 2% of children presenting with HHS at onset of type 2 diabetes.[30] HHS manifests with gradually increasing polyuria and polydipsia that may go unrecognized resulting in profound dehydration and electrolyte losses at the time of presentation. Frequently it is accompanied by lethargy, weakness, confusion, dizziness, and behavioral change.[35,263] Obesity and hyperosmolality can make the

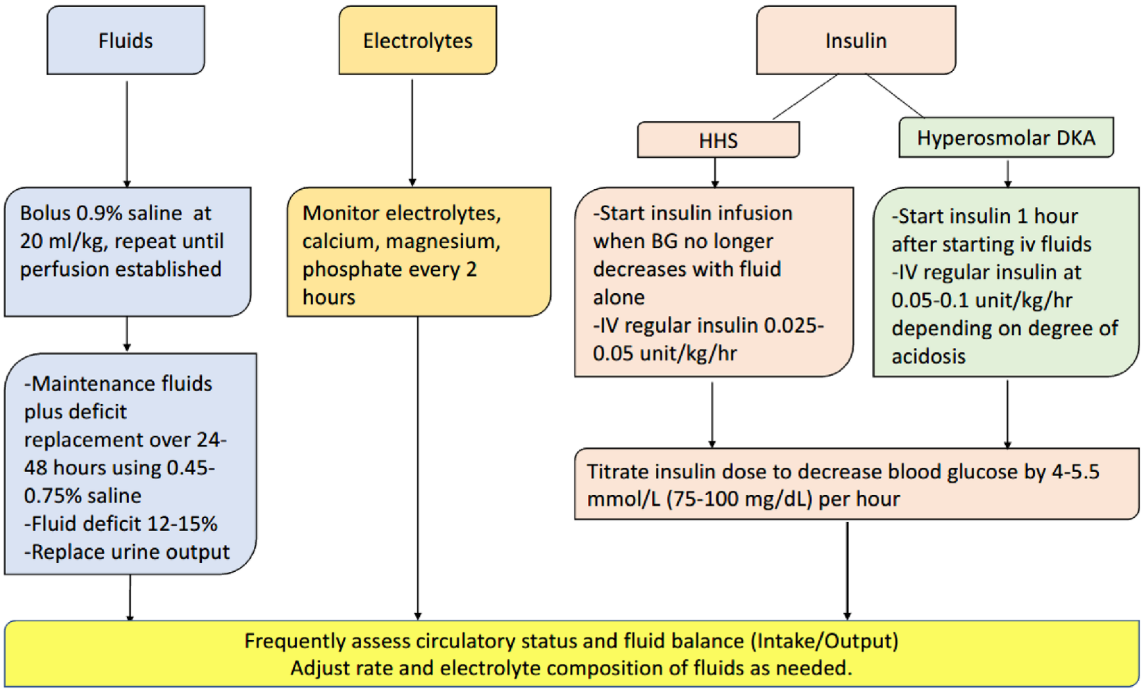

FIGURE 3 Treatment of hyperglycemic hyperosmolar syndrome (HHS)[224]

clinical assessment of dehydration challenging. Despite severe volume depletion and electrolyte losses, hypertonicity preserves intravascular volume and signs of dehydration may be less evident.

During therapy, decreasing serum osmolality results in movement of water out of the intravascular space resulting in decreased intravascular volume. In addition, pronounced osmotic diuresis may continue for many hours in children with extremely increased plasma glucose concentrations. Early during treatment, urinary fluid losses may be considerable. Because intravascular volume may decrease rapidly during treatment in children with HHS, more aggressive replacement of intravascular volume (as compared to treatment of children with DKA) is required to avoid vascular collapse.

10.1 | Treatment of HHS

There are no prospective data to guide treatment of children and adolescents with HHS. The following recommendations are based on extensive experience in adults[2] and an appreciation of the pathophysiological differences between HHS and DKA[224] (Figure 3). Children should be admitted to an intensive care unit or comparable setting where expert medical, nursing and laboratory services are available.

10.1.1 | Fluid therapy in HHS

The goal of initial fluid therapy is to expand the intra- and extravascular volume and restore normal renal perfusion. The rate of fluid replacement should be more rapid than is recommended for DKA.

- The initial bolus should be ≥20 ml/kg of isotonic saline (0.9% NaCl) and a fluid deficit of approximately 12% to 15% of body weight should be assumed. Additional fluid boluses should be given rapidly, if necessary, to restore peripheral perfusion.
- Thereafter, 0.45% to 0.75% NaCl should be administered to replace the deficit over 24 to 48 h.
- Because isotonic fluids are more effective in maintaining circulatory volume, isotonic saline should be restarted if perfusion and hemodynamic status appear inadequate as serum osmolality declines.
- Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected serum sodium concentration and osmolality.
  - Although there are no data to indicate an optimal rate of decline in serum sodium concentration, 0.5 mmol/L per hour has been recommended for hypernatremic dehydration.[264] With adequate rehydration alone (i.e., before commencing insulin therapy), serum glucose concentrations should decrease by 4.1 to 5.5 mmol/L (75 to 100 mg/dl) per hour.[265,266]
  - Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment.[35]
  - A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment due to expansion of the intravascular volume leading to improved renal perfusion. If there is a continued rapid fall in serum glucose (>5.5 mmol/L, 100 mg/dl per hour) after the first few hours, consider adding 2.5% or 5% glucose to the rehydration fluid. Failure of the expected decrease in plasma glucose concentration should prompt reassessment and evaluation of renal function.

- Unlike treatment of DKA, replacement of urinary losses is recommended.[164] The typical urine sodium concentration during an osmotic diuresis approximates 0.45% saline; however, when there is concern about the adequacy of circulatory volume, urinary losses may be replaced with a fluid containing a higher sodium concentration.

10.1.2 | Insulin therapy in HHS

Early insulin administration is unnecessary in HHS as ketosis usually is minimal and fluid administration alone causes a marked decline in serum glucose concentration. The osmotic pressure exerted by glucose within the vascular space contributes to the maintenance of blood volume. A rapid fall in serum glucose concentration and osmolality after insulin administration may lead to circulatory compromise and venous thrombosis unless fluid replacement is adequate. Children with HHS also have extreme potassium deficits; a rapid insulin-induced shift of potassium to the intracellular space can trigger an arrhythmia.

- Insulin administration should be initiated when serum glucose concentration is no longer declining at a rate of at least 3 mmol/L (~50 mg/dl) per hour with fluid administration alone.
- In children with more severe ketosis and acidosis (mixed presentation of DKA and HHS – see later), however, insulin administration should be initiated earlier.
- Continuous administration of insulin at a rate of 0.025 to 0.05 units per kg per hour can be used initially, with the dosage titrated to achieve a decrease in serum glucose concentration of 3–4 mmol/L (~50–75 mg/dl) per hour.
  - Insulin boluses are not recommended.

10.1.3 | Electrolytes in HHS

In general, deficits of potassium, phosphate, and magnesium are greater in HHS than DKA.

- Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as the serum potassium concentration is within the normal range and adequate renal function has been established.
  - Higher rates of potassium administration may be necessary, particularly after starting an insulin infusion
  - Serum potassium concentrations should be monitored every 2–3 h along with cardiac monitoring.
  - Hourly potassium measurements may be necessary if the child has hypokalemia.
- Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery.
- In children with hypophosphatemia, an intravenous solution that contains a 50:50 mixture of potassium phosphate and either potassium chloride or potassium acetate generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia.
  - Serum phosphorus concentrations should be measured every 3 to 4 h.
- Replacement of magnesium should be considered in the occasional patient who experiences severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25 to 50 mg/kg per dose for 3 to 4 doses given every 4 to 6 h with a maximum infusion rate of 150 mg/min and 2 g/h.

10.2 | Complications of HHS

- To prevent venous thrombosis, mechanical and pharmacologic prophylaxis (low molecular weight heparin) should be considered, especially in children >12 years.[224]
- Rhabdomyolysis may occur in children with HHS resulting in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling causing compartment syndrome.[221,263,267,268] The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine. Monitoring creatine kinase concentrations every 2 to 3 h is recommended for early detection.
- For unknown reasons, several children with HHS have had clinical manifestations consistent with malignant hyperthermia, which is associated with a high mortality rate.[269,270] Children who have a fever associated with a rise in creatine kinase concentrations may be treated with dantrolene, which reduces calcium release from the sarcoplasmic reticulum and stabilizes calcium metabolism within muscle cells; however, mortality rates are high, even with treatment.[269,270]
- Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare.[35] Among 96 cases of HHS reported in the literature up to 2010, including 32 deaths, there was only one instance of cerebral edema,[35] and there have been no further reports of cerebral edema in children with HHS to date. A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated.

10.3 | Mixed HHS and DKA

Mixed presentation of HHS and DKA is frequently unrecognized and managed inappropriately which may increase the risk of complications.[271] Children with mixed presentation meet criteria for diagnosis of DKA and have hyperosmolality (blood glucose concentration > 33.3 mmol/L (600 mg/dl) and effective osmolality >320 mOsm/Kg). Treatment must account for potential complications of both DKA and HHS. Mental status must be closely monitored and frequent reassessment of circulatory status and fluid balance is necessary to guide therapy. To maintain adequate circulatory volume, the rate of fluid and electrolyte administration usually exceeds that required for the typical case of DKA. Insulin is

necessary to resolve ketosis and arrest hepatic gluconeogenesis; however, insulin infusion should be deferred until the child has received initial fluid boluses and the circulation has been stabilized. Severe hypokalemia and hypophosphatemia may occur, and potassium and phosphate concentrations should be carefully monitored as described above for HHS.

CONFLICT OF INTEREST

None of the authors has any conflicts of interest relevant to the subject matter of the article.

AUTHOR CONTRIBUTIONS

All authors reviewed and summarized literature about Pediatric DKA and drafted one or more sections of the manuscript. All authors reviewed and edited the manuscript drafts. NG coordinated revisions of the manuscript based on input from ISPAD membership, the co-authors and ISPAD leadership.

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ENDNOTES

* Nitroprusside reaction method

† In the PECARN FLUID Trial, the rapid fluid infusion arm rates were calculated to replace ½ of the estimated fluid deficit over 12 h and the remaining deficit over the subsequent 24 h. As DKA typically resolves within 12 h for most children, these rates are equivalent to those calculated to replace the full deficit over 24 h in the majority. Therefore, for simplicity, we have recommended a range of 24 to 48 h for deficit replacement.

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Corrected Na in DKA

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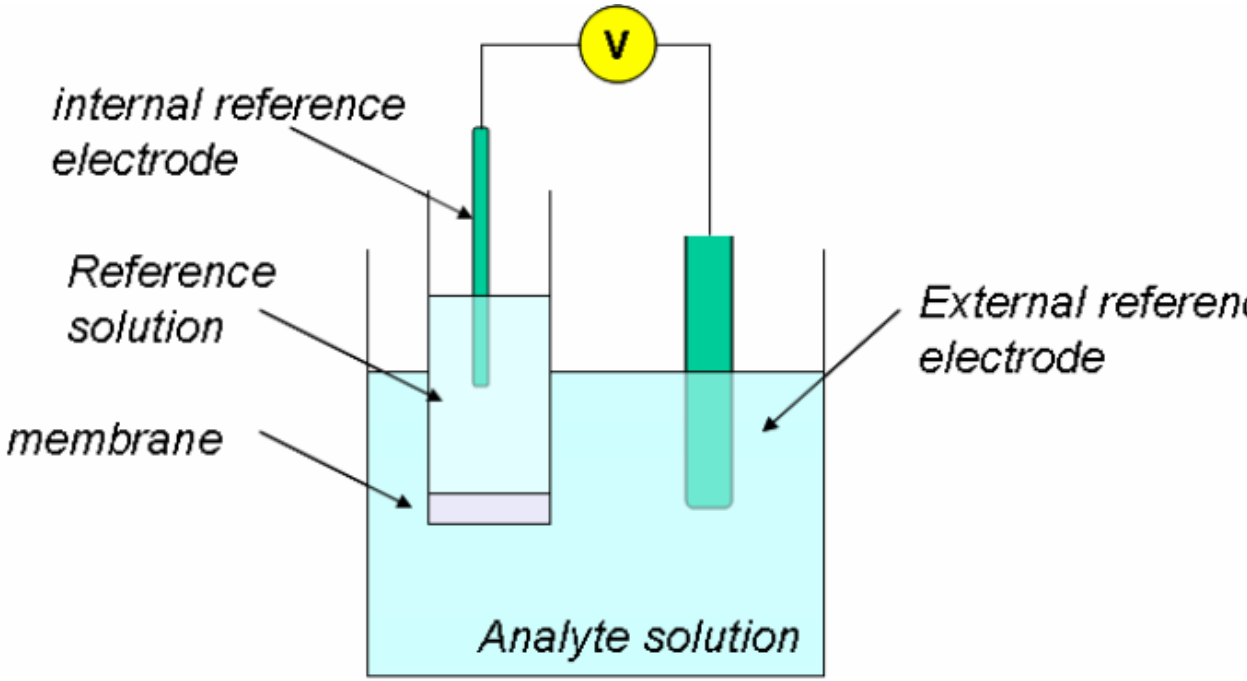
PCCL Session – January 19, 2024

Interferences in sodium assays

- Protein
- Lipids
- Glucose
- Iatrogenic – IVF, flushes

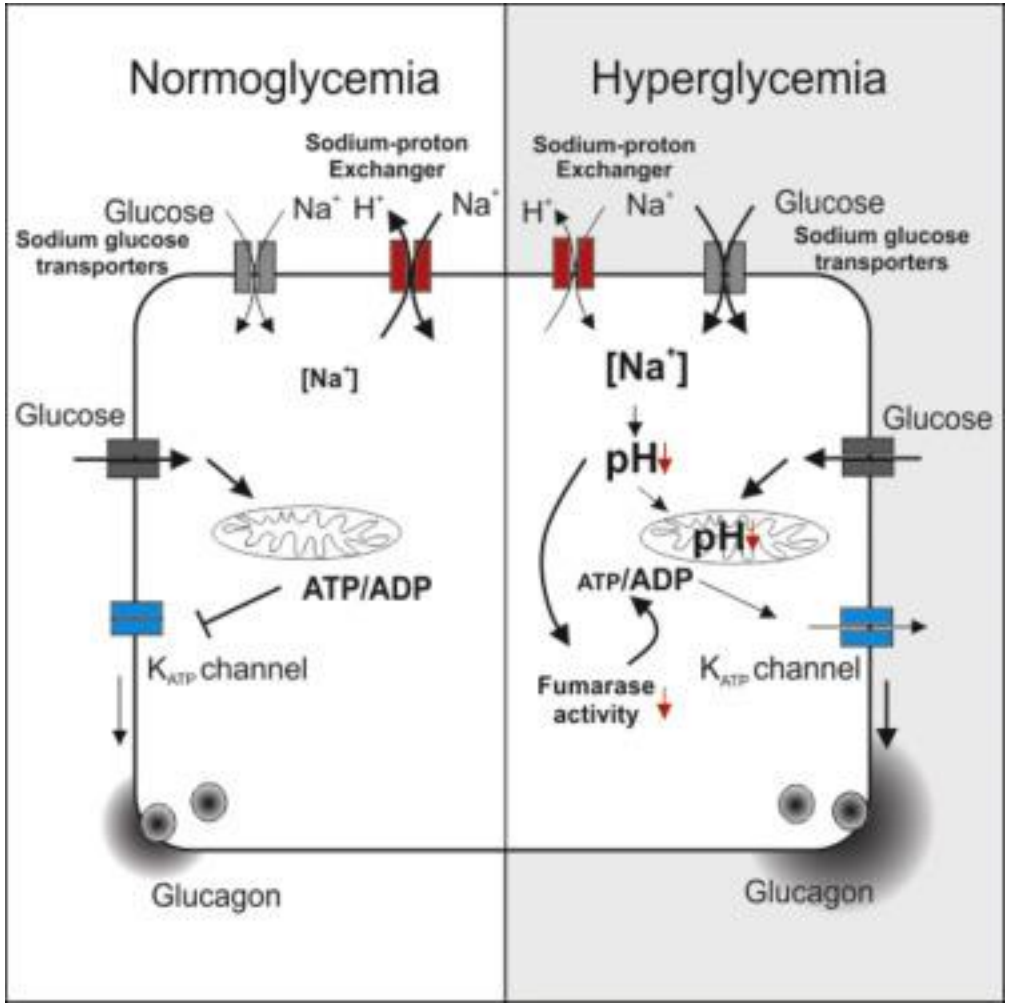
How is sodium measured?

- Isoselective Electrode (ISE)
- When a charged ion diffuses from an area of one concentration to another there is a change in energy.
- The change in energy is measured by an iso-selective electrode



Effect of glucose

- Hyperglycemia exerts osmotic pressure
- = water and Na drawn into intracellular space
- = measured serum sodium appears **normal or even low**
- Due to fluid shifts and not a decrease or loss of sodium



Corrected Na

- Those with increase blood glucose appear to have normal or even low serum sodium
- The measured Na demonstrates the sodium concentration in the intravascular space
- The corrected Na more reflective of the total body sodium