# Preventing a Drop in Effective Plasma Osmolality to Minimize the Likelihood of Cerebral Edema During Treatment of Children with Diabetic Ketoacidosis

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**Objectives** To test whether a drop in effective plasma osmolality ($P_{Eff\ osm}$; 2 × plasma sodium [$P_{Na}$] + plasma glucose concentrations) during therapy for diabetic ketoacidosis (DKA) is associated with an increased risk of cerebral edema (CE), and whether the development of hypernatremia to prevent a drop in the $P_{Eff\ osm}$ is dangerous.

**Study design** This study is a retrospective comparison of a CE group (n = 12) and non-CE groups with hypernatremia (n = 44) and without hypernatremia (n = 13).

**Results** The development of CE (at 6.8 ± 1.5 hours) was associated with a drop in $P_{Eff\ osm}$ from 304 ± 5 to 290 ± 5 mOsm/kg ($P < .001$). Control patients did not show this drop in $P_{Eff\ osm}$ at 4 hours (1 ± 2 and 2 ± 2 vs –9 ± 2 mOsm/kg; $P < .01$), because of a larger rise in $P_{Na}$ and/or a smaller drop in plasma glucose. During this period, the CE group received more near-isotonic fluids (69 ± 9 vs 35 ± 2 and 27 ± 3 mL/kg; $P < .001$). The CE group had a higher mortality (3/12 vs 0/57; $P = .003$), and more neurologic sequelae (5/12 vs 1/57; $P < .001$).

**Conclusions** CE during therapy for DKA was associated with a drop in $P_{Eff\ osm}$. An adequate rise in $P_{Na}$ may be needed to prevent this drop in $P_{Eff\ osm}$. *(J Pediatr 2007;150:467-73)*

Although cerebral edema (CE) is the most common cause of morbidity and mortality in diabetic ketoacidosis (DKA) in pediatric patients,[1-3] there is a lack of consensus on how to prevent its development.[3-6] Because CE usually occurs during the first 5 to 15 hours of treatment of DKA,[7] it is possible that therapy contributes to its development.[8] Several associations with CE have been identified, including younger age,[9] newly diagnosed diabetes,[3,9] higher initial plasma urea concentration,[1,7] higher initial plasma glucose concentration ($P_{Glucose}$),[1,9] severe acidosis,[1,7,10,11] and therapy with sodium bicarbonate.[7]

In addition to the aforementioned factors, fluid and electrolyte disturbances and their management may increase the risk of developing CE during treatment of DKA.[1,7,10-15] One important observation in this regard is that a smaller increase in the plasma sodium concentration ($P_{Na}$) during therapy is associated with CE.[7,10,15] Because $P_{Na}$ is the most important determinant of the "effective" plasma osmolality ($P_{Eff\ osm}$), our objective was to test the hypothesis that a drop in $P_{Eff\ osm}$ (defined as $2 \times P_{Na} + P_{Glucose}$) during therapy for DKA is associated with the development of CE. Furthermore, because a rise in $P_{Na}$ is necessary to maintain $P_{Eff\ osm}$ when the $P_{Glucose}$ drops, we also wanted to evaluate whether hypernatremia in this context had any untoward effects.

## METHODS

Approval was obtained from the respective institutional research ethics boards to conduct a retrospective review of patients who were admitted with DKA to the Hospital

| | | | |
|---|---|---|---|
| ANOVA | Analysis of variance | IV | Intravenous |
| CE | Cerebral edema | $P_{Eff\ osm}$ | Effective plasma osmolality |
| CT | Computed tomography | $P_{Glucose}$ | Glucose concentration in plasma |
| DKA | Diabetic ketoacidosis | $P_{Na}$ | Sodium concentration in plasma |
| HSC | Hospital for Sick Children | USP | University Hospital of São Paulo |
| ICU | Intensive care unit | | |

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for Sick Children (HSC) in Toronto or to the University Hospital of São Paulo (USP), Ribeirão Preto, Brazil.

### Definitions

To be included in the DKA population, a patient needed a $P_{Glucose} > 11$ mmol/L (200 mg/dL) and a venous pH $< 7.30$, or a plasma bicarbonate concentration $< 15$ mmol/L.[16,17] CE was defined as a clinically assessed alteration in mental status (obtundation or disorientation) in combination with radiographically or pathologically confirmed CE, or specific treatment for CE (hyperosmolar therapy and/or controlled ventilation) that was followed by prompt clinical improvement.[7] $P_{Eff\ osm}$ was calculated as $2 \times P_{Na} + P_{Glucose}$ (in mmol/L).[18]

### Study Groups

Three groups of DKA patients were included in this study. The CE group comprised all patients who developed CE during therapy for DKA and were admitted to the pediatric intensive care units (ICUs) of HSC between 1994 and 1999 or USP between 1996 and 2005. These data were collected from the 2 institutions by the same physician (APCP) to get a sufficiently large group. The characteristics of HSC and USP patients were similar (data not shown). The CE group was compared with 2 control groups of patients who did not develop CE during DKA and who were admitted to HSC in the same years as the cases. The first group (controls with hypernatremia) comprised ICU and non-ICU patients who had at least 1 $P_{Na} \geq 150$ mmol/L (hypernatremia) during the first 8 hours of hospitalization. The second group (controls without hypernatremia) comprised ICU patients who did not have hypernatremia during DKA treatment.

### Data Collection

A retrospective chart review was performed using a computer database (for ICU patients), and/or a "diabetes mellitus flow sheet" (for other departments). The first 24 hours of treatment of DKA were reviewed, starting at the point at which therapy began. Data for patients who were originally admitted to other hospitals before transfer were also included in our analysis. Data collection included biochemical and hemodynamic measures, medication, all input values (intravenous [IV] fluids and/or oral fluids, including those received at the referral hospitals), available output values, and outcome. With regard to biochemical measurements, we focused on the $P_{Eff\ osm}$, $P_{Na}$, and $P_{Glucose}$, which were recorded at 4-hour intervals; other measures are reported at the time of admission only. The amounts of sodium ($Na^+$) and potassium ($K^+$) and the volume and tonicity of the fluids (ie, amount of $Na^+ + K^+$ per liter) administered through the IV and/or oral routes were evaluated. All urinary values were analyzed, and fluid balances were calculated when data were available. Outcome measures included neurologic sequelae and mortality during or shortly after treatment of DKA.

### Statistical Analysis

Group comparisons of normally distributed variables were performed by 1-way analysis of variance (ANOVA) with least significant difference post hoc tests (with $P$ values of the latter reported). Categorical data were analyzed using Fisher's exact test (analyzing the control groups separately and together). A repeated-measures generalized linear model was used to compare changes in biochemical measures over time. A $P$ value $\leq .05$ was considered significant. Data are expressed as mean $\pm$ standard error of the mean.

## RESULTS

### Patients

The CE group consisted of 12 patients with DKA (7 from HSC and 5 from USP), who developed CE 6.8 $\pm$ 1.5 hours after therapy for DKA began (range, 0.5 to 20 hours). A total of 44 control patients with hypernatremia (peak $P_{Na}$ 161 $\pm$ 1 mmol/L) and 13 control patients without hypernatremia were also identified; all had been directly admitted to HSC. Six patients were excluded because of a central nervous system infection and/or substance abuse; an additional 11 patients were excluded because they were admitted for less than 24 hours and/or had incomplete data.

CE was diagnosed clinically in all patients in the CE group and was confirmed by computed tomography (CT) scan in 9 patients and by autopsy in 1 patient. In contrast, there was no clinical suspicion of CE in the control patients; in 3 patients, CT scans confirmed the absence of CE. Treatment for CE consisted of mannitol and ventilation in 6 patients; mannitol, hypertonic saline, and ventilation in 2 patients; hypertonic saline and ventilation in 1 patient; mannitol only in 2 patients; and ventilation only in 1 patient.

### Biochemistry Data and Hemodynamics

Biochemical and hemodynamic data for the 2 groups at the time of admission are given in Table I. $P_{Eff\ osm}$ and $P_{Na}$ were significantly higher in the control patients with hypernatremia. Other differences included a lower $P_{Glucose}$ and plasma urea and a higher hematocrit and systolic and diastolic blood pressure in the control patients without hypernatremia (Table I).

### Treatment and Outcomes

The CE group received a bolus of insulin significantly more often than the control patients (11/12 vs 9/57; $P < .001$); treatment with fluid boluses or sodium bicarbonate was comparable (Table II). Outcome was poorest in the CE group, as evidenced by a higher number of deaths (3/12 vs 0/57; $P = .003$), and a greater prevalence of neurologic sequelae (5/12 vs 1/57; $P < .001$). Neurologic sequelae included hemiparesis in 2 patients, other motor disturbances in 3 patients, visual disturbances in 3 patients, speech disturbances in 3 patients, and cognitive problems in 2 patients. One control patient developed severe hypernatremia ($P_{Na}$

**Table I. Biochemistry and hemodynamics at time of admission**

| | CE group (n = 12) | Controls with hypernatremia (n = 44) | Controls without hypernatremia (n = 13) |
|---|---|---|---|
| Plasma biochemistry | | | |
| Effective osmolality (mOsm/kg)* | 304 ± 5 | 342 ± 4† | 301 ± 2 |
| Sodium, mmol/L | 133 ± 2 | 149 ± 1† | 136 ± 1 |
| Glucose, mmol/L (mg/dL) | 38 ± 4 (684 ± 72) | 40 ± 3 (720 ± 54) | 20 ± 2‡ (360 ± 36) |
| pH | 7.09 ± 0.05 | 7.11 ± 0.02 | 7.09 ± 0.04 |
| Bicarbonate, mmol/L | 8.0 ± 1.6 | 7.7 ± 0.9 | 6.6 ± 0.8 |
| Creatinine, μmol/L (mg/dL) | 109 ± 11 (1.2 ± 0.1) | 100 ± 10 (1.1 ± 0.1) | 59 ± 8 (0.7 ± 0.1) |
| Urea, mmol/L (mg/dL) | 11.6 ± 1.2 (4.1 ± 0.4) | 10.0 ± 0.7 (3.6 ± 0.3) | 4.8 ± 0.7† (1.7 ± 0.3) |
| Hematocrit, % | 39 ± 4 | 31 ± 3 | 46 ± 2‡ |
| Hemodynamics | | | |
| Heart rate, bpm | 115 ± 7 | 137 ± 4 | 130 ± 5 |
| Systolic blood pressure, mm Hg | 107 ± 4 | 105 ± 2 | 120 ± 5‡ |
| Diastolic blood pressure, mm Hg | 67 ± 3 | 63 ± 2 | 76 ± 5‡ |

*Calculated as $2*P_{Na} + P_{Glucose}$.
†Values higher (effective osmolality and sodium) or lower (urea) compared with the 2 other groups ($P < .05$ by ANOVA).
‡Values higher (hematocrit, systolic and diastolic blood pressure) or lower (glucose) compared with the control patients with hypernatremia ($P < .05$ by ANOVA).

**Table II. Treatment and outcome characteristics**

| | CE group (n = 12) | Controls with hypernatremia (n = 44) | Controls without hypernatremia (n = 13) |
|---|---|---|---|
| Demographics | | | |
| Age, years | 6.2 ± 1.2 | 7.7 ± 0.9 | 10.8 ± 1.2 |
| Weight, kg | 21.2 ± 4.1* | 32.1 ± 3.3 | 42.5 ± 6.3 |
| Female sex, n (%) | 8 (67) | 29 (66) | 7 (54) |
| New-onset diabetes, n (%) | 6 (50) | 31 (71) | 9 (69) |
| Treatment | | | |
| Fluid bolus, n (%)† | 6 (50) | 17 (39) | 2 (15) |
| Insulin bolus, n (%)‡ | 11 (92)§ | 8 (18) | 1 (8) |
| Sodium bicarbonate, n (%) | 8 (67) | 15 (34) | 4 (31) |
| Outcome | | | |
| Neurologic sequelae, n (%) | 5 (42)§ | 1 (2) | 0 (0) |
| Mortality, n (%) | 3 (25)§ | 0 (0) | 0 (0) |

*Values lower compared with control patients without hypernatremia ($P < .05$ by ANOVA).
†Defined as ≥ 10 mL/kg in 30 to 60 minutes.
‡Defined as ≥ 0.1 U/kg in single application.
§Values higher compared with both control groups ($P < .05$ by Fisher's exact for control groups separately and combined).

increase from 149 mmol/L to 189 mmol/L) with neurologic sequelae (speech disturbances and cognitive problems).

## Course of Effective Plasma Osmolality

Figure 1 shows the time courses for changes in $P_{Eff\ osm}$, $P_{Na}$, and $P_{Glucose}$ in the 3 groups during the first 24 hours in the hospital. In the CE group, there was a significant decrease in $P_{Eff\ osm}$ in each patient as well as in the group average (304 ± 5 mOsm/kg on admission vs 290 ± 5 mOsm/kg at the time of CE; $P < .001$). The $P_{Eff\ osm}$ dropped during the first 8 hours of therapy (after which hyperosmolar therapy was given to treat CE), whereas it remained constant or decreased minimally in the control groups. This difference was statistically significant ($P = .002$), as analyzed by a generalized linear model. The drop in $P_{Eff\ osm}$ in the CE group was most prominent in the first 4 hours after admission (−9 ± 2 mOsm/kg) and was significantly greater than in the controls with hypernatremia (1 ± 2 mOsm/kg; $P = .003$) and without hypernatremia (2 ± 2 mOsm/kg; $P = .001$) (Fig 2). In the hypernatremic control patients, the small change in $P_{Eff\ osm}$ was the result of a larger rise in $P_{Na}$ (7 ± 1 vs 3 ± 1 mmol/L; $P = .03$), whereas in random control patients, it was mainly the effect of a smaller drop in $P_{Glucose}$ (−4 ± 2 vs −14 ± 2; $P = .01$) (Fig 2).

## Input and Output Values

The time interval from 4 to 8 hours was when $P_{Eff\ osm}$ reached its nadir and CE developed in most of these patients.

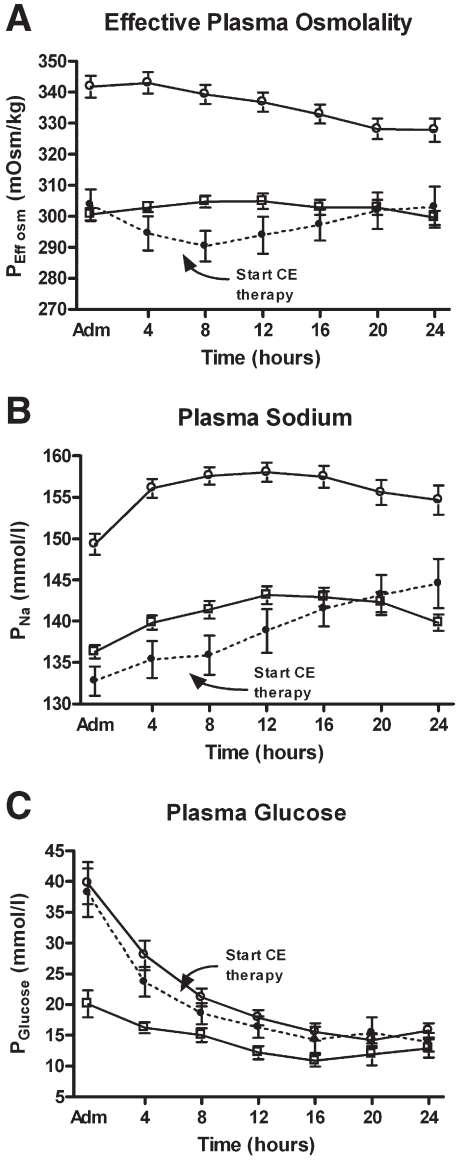


**Figure 1.** Time courses for $P_{Eff\ osm}$ (A), $P_{Na}$ (B), and $P_{Glucose}$ (C) from the start of therapy up to 24 hours of therapy, divided into 4-hour intervals. Data were available for all patients at each time point. The average time at which therapy for CE was started is indicated. —○— Controls with hypernatremia (n = 44); ···●··· CE group (n = 12); —□— Controls without hypernatremia (n = 13).

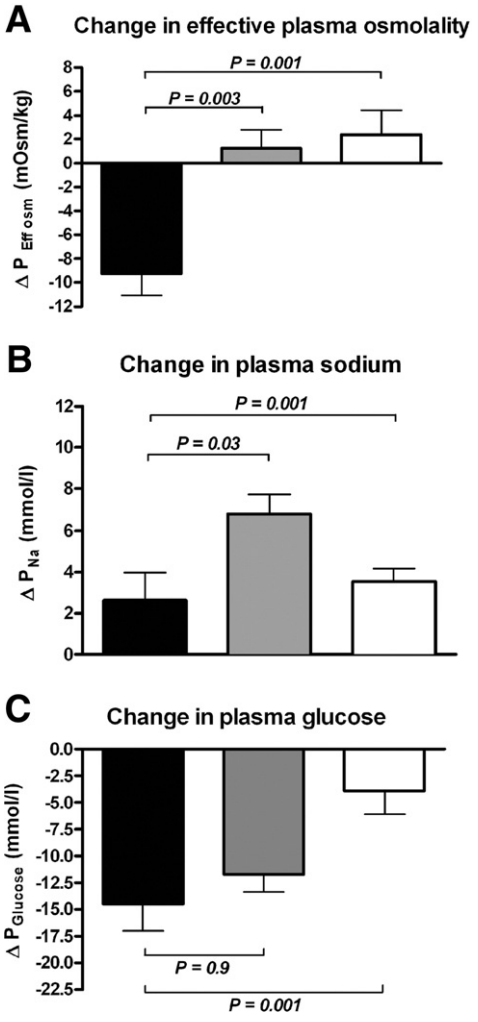


**Figure 2.** Absolute changes in $P_{Eff\ osm}$ (A), $P_{Na}$ (B), and $P_{Glucose}$ (C) during the first 4 hours of therapy. Group comparisons were performed using ANOVA and post hoc tests. *P* values from the post hoc tests are shown. (To convert glucose concentrations from mmol/L to mg/dL, multiply by 18.) ■ CE group (n = 12); ▒ Controls with hypernatremia (n = 44); □ Controls without hypernatremia (n = 13).

Therefore, we were interested in evaluating input and output values from admission until a time point within this interval (the 6-hour time point was selected). At 6 hours of therapy, the CE group received more fluid (69 ± 9 vs 35 ± 2 and 27 ± 3 mL/kg) and more $Na^+$ and $K^+$ (10 ± 2 vs 6 ± 0.5 and 4 ± 0.5 mmol/kg) compared with the control groups with and without hypernatremia (Fig 3; $P < .05$ for all). The tonicity of these fluids was lower for the CE group compared with the controls with hypernatremia (142 ± 7 vs 163 ± 4; $P = .05$). A similar analysis was performed for urinary output and balance data, which were available in 6 of the 12 CE patients, in 39 of the 44 controls with hypernatremia, and in all of the controls without hypernatremia. The CE group had a more positive balance (52 ± 19 mL/kg vs 8 ± 2 and 3 ± 4 mL/kg; $P < .001$ for both) and a higher urine output (64 ± 27 mL/kg vs 23 ± 2 and 24 ± 5 mL/kg; $P < .001$ for both) compared with the control groups. The administration of hypertonic saline to treat CE was not included in these calculations, because it was always administered after the 6-hour time point.

## DISCUSSION

Patients who developed CE had a larger drop in $P_{Eff\ osm}$ early during therapy, which was not present in controls because of either a larger rise in $P_{Na}$ or a smaller drop in $P_{Glucose}$. The changes in $P_{Eff\ osm}$ became most prominent during the first 8 hours after the start of therapy, which appeared to be a time window with a large risk for the development of CE. We also found that the CE group received a larger volume of near-isotonic fluids during this period. Finally, they had a higher urine output and a more positive fluid balance than the

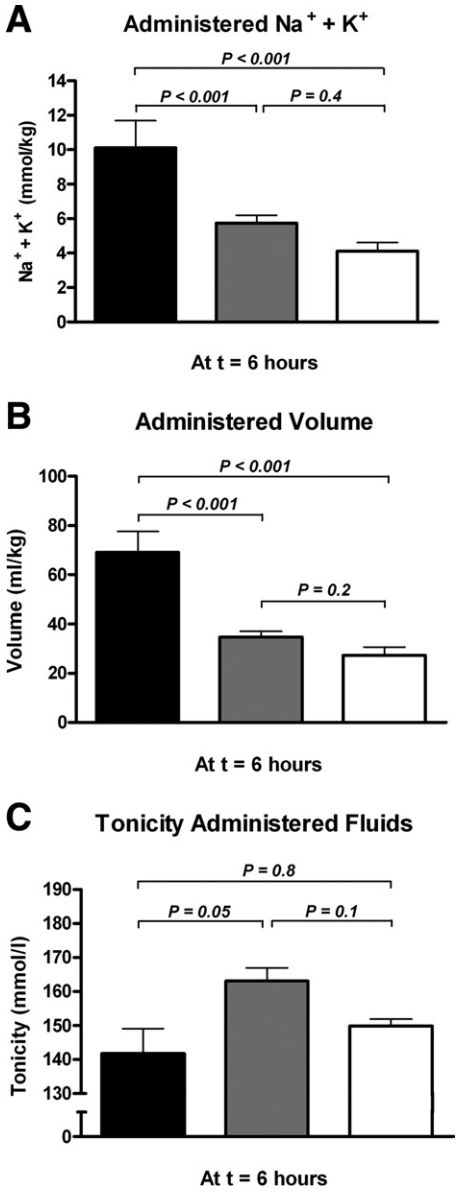


**Figure 3.** Sodium and potassium content (A), volume (B), and tonicity (C) of the fluids administered. Data are a composite of IV fluids, oral intake, and bicarbonate administration. Tonicity was calculated by dividing the $Na^+ + K^+$ content by total volume. Statistical analyses were performed by ANOVA and post hoc tests. *P* values from the post hoc tests are shown. The data represent the situation before treatment for CE. ■ CE group (n = 12); ▒ Controls with hypernatremia (n = 44); □ Controls without hypernatremia (n = 13).

control patients. Thus, this study adds to the evidence that, at least in some settings, fluid and electrolyte management during DKA might be causally linked to the development of CE.[1,7,10-15] In addition, our data confirm results from 2 previous studies, 1 by Bello et al,[9] who found that CE was related to a marked reduction in measured plasma osmolality, and the second by Durr et al,[10] who found that CE correlated with a small rise in $P_{Na}$ and a large drop in $P_{Eff\ osm}$. However, because not only osmotic factors, but also vasogenic[19] and cytotoxic factors[20] have been implicated in the formation of brain edema, we are hesitant to conclude that the large drop in $P_{Eff\ osm}$ alone caused CE. Finally, because the development of hypernatremia during DKA in patients who had near-normal $P_{Na}$ values on admission prevented a large drop in $P_{Eff\ osm}$ and was associated with better outcome, it might be a goal of therapy for this subset of patients.

The next important issue is to define how fluid and electrolyte management may have caused the large drop in $P_{Eff\ osm}$ in the CE group. We consider 4 possibilities based on the available evidence. First, the drop in $P_{Eff\ osm}$ may have been caused by increased infusion of IV fluids with a lower $Na^+ + K^+$ concentration.[21] Because the tonicity of the infusate was somewhat hypotonic to the patients, the infusion of larger volumes may have resulted in a positive electrolyte-free water balance, which prevented an adequate rise in $P_{Na}$ in the face of decreasing $P_{Glucose}$ levels.

Second, if the infused volume was sufficiently high to cause expansion of the extracellular fluid volume, this may have triggered a "desalination" process.[22] To produce a drop (or a smaller rise) in $P_{Na}$ in these patients, a negative balance for $Na^+ + K^+$ and/or a positive balance for water must be achieved. What is known about the composition of the urine in patients with DKA is that the $Na^+$ concentration in the urine is ~40 to 50 mmol/L during the osmotic diuresis phase.[23] Nevertheless, once the $P_{Glucose}$ drops appreciably, glucosuria diminishes, and the $Na^+ + K^+$ concentration in the urine can rise appreciably. It is at this time that desalination of infused saline could contribute to the smaller rise in the $P_{Na}$. Of relevance, patients who developed CE in our study received almost twice as much intravenous saline.

Third, although not obvious on clinical grounds, a factor that merits attention is the role of hypotonic fluid retention in the upper gastrointestinal tract. When fruit juice and/or sweetened pop are ingested, there may be a large volume of water with little $Na^+$ in the stomach, and its rate of emptying could be rapid early during therapy, as described in a previous case.[24] If the CE group drank predominantly water before coming to the hospital and their stomach emptying was more rapid, this may have caused a smaller rise in the $P_{Na}$.

The fourth potential contributing factor to CE identified in this study was the higher incidence of insulin bolus administration. Giving a bolus of insulin activates the sodium: hydrogen ion ($H^+$) exchanger,[25] resulting in a gain of $Na^+$ and a loss of $H^+$ in the intracellular fluid compartment. This results in an increased number of intracellular solutes, because exported $H^+$ will be largely bound to intracellular buffers. This increase in the number of solute molecules inside cells could expand the intracellular volume, because water moves rapidly across cell membranes to achieve osmotic equilibrium. This could explain how insulin bolus administration could contribute to CE, especially when insulin was given at the onset of treatment, when the blood-brain barrier might be more permeable.[26-28]

Clinically, an important question is how these ideas could aid in optimizing fluid and electrolyte management in

pediatric patients who present with DKA. The 2 major goals of IV fluid therapy should be to deal with hemodynamic emergencies due to low extracellular fluid volume (at the outset recognizing that true emergencies are not common) and to avoid a rapid drop in $P_{Eff\ osm}$ to minimize the risk of developing CE.[16,17,29]

With regard to the first goal, based on the available biochemical and hemodynamic data on admission, it is questionable that there was a hemodynamic indication to infuse such a large amount of $Na^+ + K^+$. For example, the amount of infused $Na^+ + K^+$ in the CE group exceeded 9 mmol/kg, roughly equal to 30% of the extracellular fluid volume.[28] Thus a more moderate fluid regimen may be advisable if there is no compelling evidence to warrant being aggressive.[15,30-33] We previously showed that the degree of extracellular fluid contraction during hyperglycemia is best assessed by serial plasma hematocrit or total protein levels;[34] thus, these should be determined more frequently during fluid resuscitation in DKA.

With regard to the second goal, the $P_{Eff\ osm}$ was not well maintained in the patients who developed CE. Regularly assessing $P_{Eff\ osm}$ and paying more attention to the urine volume and its electrolyte concentrations in these potentially vulnerable groups might help define whether the $P_{Eff\ osm}$ is likely to drop. In addition, a low $P_{Na}$ on admission may serve as a warning sign. If $P_{Eff\ osm}$ drops, infusing an appropriate volume of hypertonic saline is a therapeutic option to consider.[35] Because the $P_{Eff\ osm}$ was remarkably well maintained in the control patients, the development of hypernatremia might be needed in those patients with a high $P_{Glucose}$ and near-normal $P_{Na}$ to prevent an excessive drop in the $P_{Eff\ osm}$ early in therapy. This is further supported by the good clinical outcome and few adverse events in all but 1 unusual case, in which a lesser rise in $P_{Na}$ and a small drop in $P_{Eff\ osm}$ may have been needed. We speculate that most of the control patients developed hypernatremia because they either had a greater osmotic diuresis (with the consequent loss of more electrolyte-free water) and/or received isotonic fluids while excreting a hypotonic urine.[18] Another way to maintain $P_{Eff\ osm}$ is to establish a smaller drop in $P_{Glucose}$, as occurred in the controls without hypernatremia, although it must be noted that these patients' degree of hyperglycemia on admission was less severe.

Because of the descriptive nature of this study, some limitations should be mentioned. First, the study was designed to test a single hypothesis in relation to CE, and thus other factors were not weighed in a multivariate approach. Second, the way in which cases and controls were selected does not allow a representative estimate of the incidence of CE and hypernatremia during DKA.

In conclusion, this study suggests that the production of a modest degree of hypernatremia might be needed to prevent a drop in $P_{Eff\ osm}$ and the development of CE in children with DKA. This may explain why a smaller rise in $P_{Na}$ might be associated with CE.[7,10,15] If a drop in $P_{Eff\ osm}$ were prevented during therapy of DKA, and this required the presence of hypernatremia, then perhaps achieving this abnormal electrolyte concentration should be a goal of therapy when $P_{Na}$ is not appreciably low in a patient with serious hyperglycemia.

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# 50 Years Ago in *The Journal of Pediatrics*

## Serious complications of varicella, including fatalities

Blattner RJ. J Pediatr 1957;50:515-18

In 1957, Blattner reported on the recognition of serious complications of varicella-zoster virus (VZV) infection in children. He reviewed known complications of VZV infection but also commented on pathologic and clinical findings described in the deaths of 2 immunocompromised children. Both cases demonstrated diffuse vasculitis and acute encephalitis at autopsy, constituting an early description of severe central nervous system complications of varicella.

What we know now about VZV prevention, treatment, and outcomes helps put these early findings into perspective. The most significant development in the management of VZV infection was the development of a live, attenuated varicella vaccine, licensed in 1996 and recommended in 1997 for routine vaccination of susceptible children aged 12 to 18 months. According to a 2003 report by the Centers for Disease Control, national varicella vaccination rates increased from 26% in 1997 to 85% in 2003 for children aged 19 to 35 months. Simultaneously, the incidence of acute chickenpox infection in the United States decreased ≤84% between 1990 and 2001 in reporting states. A 70% decline in varicella hospitalization rates from 1995 to 2003 and a 78% decline in varicella-related deaths for all age groups during 1999 to 2001, as compared with 1990 to 1994, were documented in 2 regional reporting sites. Efforts to provide booster doses of vaccine to prevent breakthrough infection and utilization of an adult zoster vaccine will likely further reduce VZV-related morbidity.

Immunocompromised children with acute VZV infection suffer disproportionate morbidity and death relative to healthy children. Encephalitis, hepatitis with fulminant liver failure, and pneumonitis remain deadly. Advances in prevention and treatment, including the use of vaccine, varicella-zoster immune globulin, and antiviral therapy have led to reductions in mortality rates for these patients. However, rates of solid organ transplantation, HIV infection, and use of immunosuppressive therapy have increased dramatically since 1957, and opportunistic infection remains the most common cause of death for immunocompromised patients. Thus, public health initiatives toward primary prevention of VZV infection must be prioritized. There remains great variation in immunization rates across states, as well as wide variation in immunization requirements for school and child care entry, which may constitute lost opportunities for disease prevention.

Whereas great progress toward reducing the burden of VZV infection in children has occurred since Blattner's report in 1957, the rate of death associated with severe varicella-related complications remains significant, especially for immunocompromised patients. Care must be taken not to forget that these dangers remain just as scary and real as they were in 1957.

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