noted, however, that studies such as theirs cannot be used to derive entirely "safe" quantities of fluid and insulin or to impute pathophysiology, but rather can only suggest general treatment principles.[6]

Prudent fluid replacement therapy individualized to the severity of dehydration and osmolality is appropriate for treating DKA, as is currently recommended. Other recommendations include to avoid administering insulin boluses and to begin infusion 1 to 2 hours after starting fluid replacement therapy.[7] The editorial accompanying the article by Hoorn et al suggests the need to revise the 2004 consensus statement from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society that notes a lack of evidence of a relationship between the volume or sodium content of intravenous fluid and the development of CE, as well as the uncertainty regarding the association of the risk of CE with an attenuated rise in serum sodium concentration during therapy.[8] Analysis of the study of Hoorn et al alongside true case-control investigations involving more than 6 times as many cases, as well as contradictory findings in a similar study involving nearly twice the number of cases from the same milieu, provides no basis for a change in this statement. The more recent Clinical Practice Consensus Guidelines for Diabetic Ketoacidosis from the International Society for Pediatric and Adolescent Diabetes reinforce the conclusion that there is no convincing evidence of an association between the rate of fluid or sodium administration used to treat DKA and the development of CE.[7]

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Reply

To the Editor:

We are pleased to respond to the comments on our article expressed in the foregoing three letters. Two of the letters raise concerns regarding the case-control design of our study, one letter claims to have found an error in the reported fluid retention, and finally, one letter suggests a role for unmeasured osmolytes. Here we respond to each letter individually, although several of our comments also refer to the other two letters and to diabetic ketoacidosis (DKA) and cerebral edema (CE) in general.

Response to Drs Glaser and Kuppermann

We readily agree that our study did not apply a rigorous matched case-control study design, as we noted earlier.[1] Our intention was to describe and compare 3 selected case series of DKA. We did this to investigate the potential importance of preventing a drop in the effective plasma osmolality ($P_{Eff\ osm}$) and thereby the need for a rise in the plasma sodium concentration by a predictable amount when the plasma glucose concentration drops, even if this means that hypernatremia must be present. These aspects have not been studied to date.

We doubt that this approach affected our main conclusion, because even without comparison to control groups, the drop in $P_{Eff\ osm}$ was already obvious and significant in a paired *t* test shortly after therapy began.[1] We actually believe that our data correspond fairly well with those of Glaser et al.[2] Both studies demonstrate an association between a smaller rise in plasma sodium concentration and the development of CE.[1,2] Our study may provide a pathophysiologic explanation for these observations; if cases have a smaller rise in their plasma sodium concentration, then there is less counterbalance for decreasing glucose levels, and thus the $P_{Eff\ osm}$ is more likely to drop. Central to our reasoning is the reliance on physiological principles rather than on isolated risk factors.

We extrapolate this comment to previously published case-control studies that have analyzed the infusion of intravenous fluids. First, dehydration has not been controlled for in any study. Simply put, clinicians cannot quantify the degree of extracellular fluid (ECF) volume contraction based on physical examination only.[3,4] Even including measures of body weight is still not satisfactory, because the degree of catabolism (loss of intracellular fluid [ICF]) and the weight of gastric and intestinal contents cannot be assessed. The only way to obtain a quantitative index is to use the hematocrit/hemoglobin and albumin/total protein concentrations in plasma, and even these are not perfect.[5] Based on an analysis of hematocrit values, our CE patients were not more "dehydrated," as was suggested by Drs Glaser and Kuppermann, who relied on urea levels only. In summary, we believe that all studies that claim to have controlled for "dehydration" did not actually do so.

Second, in terms of the judiciousness of fluid replacement, without a reliable index of the degree of ECF volume contraction, on what basis can one be confident that the intravenous fluid prescription was judicious? In more detail, it

is important to recognize that normal subjects do not have a normal ECF volume; rather, they have an expanded ECF volume, to signal the kidney to excrete the extra sodium that they ingest each day. In addition, it is not the ECF volume that is important for hemodynamics; rather, it is the degree of contraction of the "effective" arterial blood volume, which depends also on the tone and contraction of the venous capacitance vessels and on myocardial contractility.

Third, in terms of controlling for acid-base disorders, relying on arterial blood values or venous blood values assuming a constant pCO_2 difference between arterial and venous pCO_2 measurements, as was done in 1 major study,[2] does not provide an adequate assessment of the danger of metabolic acidosis.[6-8] A much better pathophysiologic analysis involves using brachial venous pCO_2 to determine whether the bulk of the H^+ load was buffered safely (eg, using HCO_3 in the ECF and ICF compartments of skeletal muscle) or whether a larger H^+ load was exported to the brain for removal by binding to intracellular proteins in this organ.[6-8] Because this has not been done in any study in young patients with DKA, this factor also has not been evaluated in any reported series of patients.

With regard to the presumed error in the reported fluid retention, Drs. Glaser and Kuppermann argue that because the mean fluid administration was 69 mL/kg and the urine output was 64 mL/kg, the retained fluid more likely would be 5 mL/kg instead of the reported 52 mL/kg. Unfortunately, they appear to have misread the article and thus used 2 different sets of numbers. As we clearly stated, balance data were available for only 6 of the 12 CE patients;[1] therefore, 69 mL/kg refers to the administered fluid in all 12 CE patients, whereas the positive fluid balance of 52 mL/kg and the urine output of 64 mL/kg refer to the available balance data in the 6 patients for whom data were available, demonstrating that they received even more fluids.

Response to Drs Sema and Puliyel

Drs Sema and Puliyel raised 2 points that merit discussion:

1. The CE group had a lower plasma sodium concentration than that observed in the control groups: Those patients who developed CE and had the lower plasma sodium concentrations may have greater brain cell volume and thus a potentially greater risk of developing CE during therapy. One other point should be mentioned in this context. We do not know the glucose concentration in brain cells, recognizing that brain cells represent a mixture of neurons (the minority) and several distinct types of non-neurons (the majority). Thus, even though we used the $P_{Eff\ osm}$ formula in our analysis, this might not provide a truly quantitative analysis of the change in ICF volume in all of the cells in the brain. For example, direct infusion of glucose or urea into the carotid artery produced little if any release of vasopressin, but hypertonic saline infusion caused a rise in vasopressin release.[9] These data suggest that the $P_{Eff\ osm}$ in cells of the osmostat are far less sensitive to the glucose concentration than to the plasma sodium concentration in the $P_{Eff\ osm}$ formula. Consequently, future studies should include a more in-depth analysis of these points.
2. Ketoacid accumulation may raise the $P_{Eff\ osm}$. In terms of the pH of blood in patients with DKA, <1% of the $P_{Eff\ osm}$ is the sum of the undissociated ketoacids. Therefore, its contribution to the osmolality in the ECF and ICF compartments is too small to play an important role in osmolality. When analyzing the effects of ketoacid anions, we cannot examine their effect alone—we also must include an analysis of the effects of the added H^+ as well. Most of the added H^+ will be removed by reacting with HCO_3^-, and the resulting CO_2 will be exhaled.[7] Because most of the H^+ accompanying β-HB^- anions should remove HCO_3^-, the gain in β-HB^- anions should be equal to the loss of HCO_3^-, and there would be no change in the $P_{Eff\ osm}$. Only the small proportion of H^+ that binds to proteins, resulting in more cationic proteins and new β-HB^-, would raise the $P_{Eff\ osm}$. But even then, the effect would be half that of a change in the plasma sodium concentration. For this to be quantitatively important in plasma, we would need plasma proteins with a substantial increase in positive charge. In fact, the net rise in cationic voltage per 0.1 pH unit fall is quite small, but it may become important if the blood pH is clearly <7.0.[10] Therefore, this point could have merit in a subset of patients with very severe acidemia.

Response to Dr Rosenbloom

Dr Rosenbloom takes issue with our main conclusion about the importance of the effect of intravenous fluid administration on a change in the $P_{Eff\ osm}$ and its potential implication for the development of CE, because previously published case control series did not reach a similar conclusion. Those studies that provided data on the difference in osmolality between cases and controls did not use $P_{Eff\ osm}$, because urea was included in the calculation.[2,11] This practice is physiologically unsound, however, because urea passes quickly between the ECF and ICF compartments, and thus does not influence water shifts.

The study of Muir et al[12] provided no information on how osmolality was calculated and whether it differed between cases and controls. The only study in which $P_{Eff\ osm}$ was calculated compared the values only at presentation and did not enter them into their linear regression model for the risk of CE.[13] Furthermore, none of these studies provided a similar detailed analysis of the tonicity of intravenous fluids (Na + K per liter) that we collected starting at the initiation of treatment, which frequently begins outside the tertiary referring center. We also feel that our hypothesis is supported by the dramatic effect of reversing clinical symptoms of impending brain stem herniation that we and others have documented by rapidly raising the $P_{Eff\ osm}$ by the infusion of 3% saline in patients with DKA and CE.[14,15]

Although no prospective human studies are available to support our hypothesis, there is a well-designed animal study

that has investigated the relationship among $P_{Eff\ osm}$, tonicity of fluids, and cerebral edema in DKA and included measurements of intracranial pressure (ICP).[16] This study found that as $P_{Eff\ osm}$ decreased, due to rapid administration of low-tonicity fluid, the ICP rose. In contrast, the ICP did not rise when the $P_{Eff\ osm}$ remained constant.

The consensus statement publications that addressed the issue of intravenous fluids in the genesis of CE were based on evidence in the published literature at that time. Our study provides new evidence of the importance of the tonicity of the intravenous fluid chosen to replace the deficit and the importance of preventing an overly rapid drop in $P_{Eff\ osm}$ when the glucose concentration in plasma decreases. We feel that the statement in the discussion section of our article that "our 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" is both appropriate and supported by the data. We also emphasize that CE is a complication with many risk factors, each of which needs to be minimized to prevent inducing this dreaded complication.[17]

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