

Is Fluid Therapy Associated With Cerebral Edema in Children With Diabetic Ketoacidosis?

Jeffrey Hom, MD, MPH
Richard Sinert, DO

From the Department of Emergency Medicine, SUNY–Downstate Medical Center, Brooklyn, NY.

Study objective: Diabetic ketoacidosis is the most common cause of morbidity and mortality in children with type I diabetes mellitus, and cerebral edema is the leading cause of pediatric diabetic ketoacidosis death. Excessive intravenous fluid administration has been implicated as a cause of cerebral edema. We perform an evidence-based emergency medicine review assessing the association of intravenous fluid hydration and cerebral edema.

Methods: We searched MEDLINE and EMBASE for comparative studies. Because of the low incidence of cerebral edema, we included observational studies in our review. We sought studies including patients younger than 18 years and with diabetic ketoacidosis. We defined cerebral edema, using clinical, radiographic, pathologic criteria, or treatment for intracranial pressure.

Results: Three studies met criteria for this review, of which 2 used fluid volume/body weight per unit of time, and the third measured cumulative total volume during hourly periods. The first 2 studies showed no statistically significant association between intravenous fluid administration and cerebral edema. The third study showed a significant association (odds ratio 6.55; 95% confidence interval 1.38 to 30.97) between the total volume (uncorrected for body weight) of infused fluid and the risk of cerebral edema.

Conclusion: Accepting the inherent limitations of observational studies, we found a lack of strong or consistent results implicating rate or volume of fluid administration as a precipitant cause of cerebral edema in patients with diabetic ketoacidosis. [Ann Emerg Med. 2008;52:69-75.]

0196-0644/\$-see front matter

Copyright © 2008 by the American College of Emergency Physicians.

doi:10.1016/j.annemergmed.2008.01.330

CLINICAL SCENARIO

You are working the late night shift in a local emergency department (ED). A 6-year-old boy is brought in by his mother, who tells you her child is “sick.” You obtain a history of profuse vomiting for the last 48 hours. The mother attributes this to “stomach flu.” The boy complains about abdominal pain for the last few hours.

The patient’s vital signs at triage are blood pressure of 80/50 mm Hg and pulse rate of 140 beats/min. A bedside dextrose fingerstick result is greater than 600 mg/dL. The child responds appropriately to your questions. You notice his breath has a fruity odor and that he shows signs of clinical dehydration, including dry mucosa membranes, skin tenting, and a capillary refill greater than 4 seconds.

After providing the child with a cardiac monitor, establishing an intravenous line, sending appropriate tests for laboratory evaluation, and starting an initial bolus of 20 mL/kg normal saline solution to correct dehydration, you receive blood gas and metabolic panel results showing a pH of 7.00 and Na 135 mEq/L, K 4 mEq/L, Cl 98 mEq/L, HCO₃ 9 mEq/L, blood urea

nitrogen (BUN) 50 mg/dL, creatinine 1.5 mg/dL, and glucose 900 mg/dL.

You diagnose diabetic ketoacidosis and put a call out to the pediatric ICU to arrange transfer. You decide this patient will require maintenance fluids, along with additional intravenous fluid, for an estimated 10% dehydration. You plan to give this total amount during a 24-hour period and start an insulin drip at 0.1 units/kg per hour. The pediatric ICU attending physician calls back but considers your fluid administration plan to be aggressive and suggests that the rate be slowed down because of the risk of cerebral edema in pediatric diabetic ketoacidosis patients. You are unsure of the validity of this concern.

The following evidence-based emergency medicine review seeks an answer to the question posed by this scenario.¹

FORMULATING THE QUESTION

In formulating the question for this review, we were interested in whether aggressive intravenous fluid hydration increases the risk of cerebral edema in pediatric patients with

diabetic ketoacidosis. Though the incidence of cerebral edema is low, about 1% among those with diabetic ketoacidosis, it is the most common cause of mortality, accounting for 57% to 87% of all pediatric diabetic ketoacidosis deaths.²

We defined the pediatric age group to be children younger than 18 years. We chose a definition of diabetic ketoacidosis by using biochemical criteria: blood glucose level greater than 200 mg/dL, with venous pH less than 7.3 or bicarbonate less than 15 mmol/L, and ketosis.² We questioned whether pediatric patients with diabetic ketoacidosis complicated by cerebral edema (outcome of interest) received higher volumes and rates of intravenous fluids (exposure) than those children with diabetic ketoacidosis but not developing cerebral edema (comparison). The amount of fluid given would ideally be calculated with a weight-based formula addressing acute resuscitation, deficits from dehydration, and maintenance. The outcome of interest to clinicians and patients is the development of cerebral edema during the first 24 hours of treatment of diabetic ketoacidosis. To qualify as a case of cerebral edema, a patient needed to have a depressed level of consciousness or an alteration of mental status, with or without confirmatory brain computed tomographic scan, or to have received specific treatment for cerebral edema (hyperosmolar therapy or controlled hyperventilation). To be potentially associated with initial volume or rate of intravenous fluids administered, we required clinical manifestations of cerebral edema to be reported within the first 24 hours of treatment of diabetic ketoacidosis.

We formulated our complete clinical question as, Is intravenous fluid therapy given to pediatric patients with diabetic ketoacidosis during the first 24 hours of treatment associated with an increased risk of clinically significant cerebral edema?

SEARCHING FOR AND SELECTING THE BEST EVIDENCE

Our question is whether a greater compared to a lesser rate of fluid resuscitation and replacement is associated with an increased incidence of acute cerebral edema among pediatric patients presenting to the ED with diabetic ketoacidosis. If such an association were consistently found in severity-adjusted observational studies or randomized trials, we would be inclined to choose relatively lower rates of fluid administration, even in the early phases of treatment. Because of the low incidence of cerebral edema in this population (0.68% to 3%),² we suspected that the highest level of evidence addressing our question would stem from observational studies. We therefore considered all analytic studies, including cohort and case-control studies, of pediatric diabetic ketoacidosis that reported on the association between volume of fluid administration over time and acute cerebral edema.

We searched MEDLINE with the PubMed interface from 1966 to January 2007 and EMBASE from 1980 to January 2007 with the Ovid Technologies interface (see Appendix E1 for complete MEDLINE and EMBASE search strategies; available online at <http://www.annemergmed.com>). We also

searched the Cochrane Central Register of Controlled Trials, using the same MEDLINE search strategy and the bibliographies of the included and relevant articles and reviews. We hand searched bibliographies of relevant articles and reviews but did not search for abstracts in key journals or unpublished studies.

The MEDLINE search gave 107 results; the EMBASE search gave 50 results that were unique to this search engine, yielding a total of 157 articles. No randomized controlled studies were found. We excluded case reports, case reviews, case series, commentaries, and nonsystematic reviews. On this basis, 148 articles were eliminated from this review.

From the remaining 9 articles, we excluded 3 because they lacked a control group.³⁻⁵ After full article review, we excluded an additional 3 articles⁶⁻⁸ because they did not allow a direct comparison between patients receiving specific volume rates with respect to the onset of cerebral edema. As a result, our short-cut evidence-based emergency medicine review included 3 case-control studies, by Edge et al,⁹ Glaser et al,¹⁰ and Lawrence et al.¹¹ The chief advantage of case-control studies is that they are an efficient method to study rare events because you can identify a group of patients who have already experienced the outcome of interest and then retrospectively collect information about a particular exposure.

ANALYZING THE EVIDENCE

Description of the Studies

Table 1 summarizes the key features of the 3 reviewed case-control studies. Edge et al⁹ and Lawrence et al¹¹ identified their subjects from a previously established prospective population-based surveillance of pediatricians for rare childhood diseases in the United Kingdom and Canada, respectively. Glaser et al¹⁰ used a retrospective study design to find their subjects in 10 hospitals in the United States. The enrollment periods for the 3 reviewed studies were as follows: Edge et al⁹ (1995 to 1998), Glaser et al¹⁰ (1982 to 1997), and Lawrence et al¹¹ (1999 to 2001).

To increase the likelihood of finding cases, Lawrence et al¹¹ asked pediatricians in their country's surveillance program to specifically report any deaths among diabetic patients. Edge et al⁹ established a separate national reporting system for cases of diabetic ketoacidosis to assist with identification of controls.

Edge et al⁹ defined cerebral edema as requiring a deterioration of mental status, with clinical criteria associated with increased intracranial pressure (hypertension and bradycardia, breathing pattern abnormalities, squint, blurred disc margin, decerebrate or decorticate posturing, respiratory arrest). Neither Glaser et al¹⁰ nor Lawrence et al¹¹ mention the use of specific clinical criteria to define cerebral edema.

Controls for the reviewed studies were children with diabetic ketoacidosis but without cerebral edema. All studies used similar criteria to define diabetic ketoacidosis according to low pH or bicarbonate (if pH not available) in the presence of ketonuria.

The 3 studies reported different measures of fluid administration. Glaser et al¹⁰ and Lawrence et al¹¹ defined

Table 1. Summarizing the characteristics of 3 case-control studies of cerebral edema in pediatric diabetic ketoacidosis.

Study	Patients	Fluid Therapy as Risk Factor for Cerebral Edema
Edge et al 2006 ⁹	<p>Age: <16 y (mean=8.5)</p> <p>DKA: Decompensated diabetes mellitus with pH <7.3, or plasma bicarbonate level <18 mmol/L, or heavy ketonuria</p> <p>Cases (n=43)</p> <p>Cerebral edema: Deterioration in the level of consciousness and associated clinical evidence of increased intracranial pressure or radiographic evidence or postmortem evidence.</p> <p>Identified by prospective surveillance by pediatricians in England, Scotland, and Wales during 3-y period, confirmed by record review.</p>	<p>Exposure:</p> <p>Cumulative volume (not weight-based) of intravenous fluid given during the first 4 h of therapy for DKA, stratified by volume cutoff range.</p> <p>Comparison between DKA with and without cerebral edema:</p> <p>Unconditional logistic regression models including biochemical and treatment related variables (including cumulative fluid infusion volume).</p>
Glaser et al 2001 ¹⁰	<p>Age: <18 y (mean=9)</p> <p>DKA: pH <7.25 or serum bicarbonate <15 mmol/L, ketonuria and serum glucose concentration >300 mg/dL</p> <p>Cases (n=61)</p> <p>Cerebral edema: Alteration in mental status and radiologic or pathologic evidence, or given treatment consistent with cerebral edema.</p> <p>Identified by retrospective review in 10 US pediatric centers during 15-y period.</p>	<p>Exposure:</p> <p>Fluid infusion rates measured as increments of 5 mL/kg per h during the interval to appearance of cerebral edema for each case.</p> <p>Comparison between DKA with and without cerebral edema:</p> <p>Conditional logistic regression model including demographics, initial and changes in biochemical values, and therapeutic variables (including fluid infusion rates)</p>
Lawrence et al 2005 ¹¹	<p>Age: <16 y (mean=9)</p> <p>DKA: pH <7.35 or low bicarbonate with diabetes and ketonuria</p> <p>Cases (n=17)</p> <p>Cerebral edema: sudden or unexpected deterioration in level of consciousness.</p> <p>Identified by prospective surveillance by Canadian pediatricians during 2-y period (13) with additional cases located through record review (8)</p>	<p>Exposure:</p> <p>Fluid infusion measured as mL/kg per h during treatment interval before appearance of cerebral edema for each case.</p> <p>Comparison between DKA with and without cerebral edema:</p> <p>Two different logistic regression models were used to assess the risks of cerebral edema in DKA patients. The first model included demographic and treatment variables (including infusion rates). The second model used only BUN and fluid infusion rates to test whether higher infusion rates were a reflection of the severity of illness.</p>

DKA, Diabetic ketoacidosis.

intravenous fluid administration as the volume infused per kilogram of body weight per hour. Edge et al⁹ reported total infused volume uncorrected for body weight and reported quantitative results during the 4 hours of resuscitation. Glaser et al¹⁰ analyzed the difference between fluid administration as mL/kg per hour and reported those data in terms of increments of 5 mL/kg per hour between those diabetic ketoacidosis patients with and without cerebral edema for the interval between onset of treatment and recognition of cerebral edema. Edge et al⁹ reported the total amount of intravenous fluid, divided into tertiles of total administered volume (uncorrected by body weight) by time; odds ratios for developing cerebral edema were calculated within the intravenous fluid volume tertiles for

intervals extending to 4 hours from initiation of therapy. None of the 3 included studies reported on the type of fluid (isotonic/hypotonic) used or the use of potassium, which may alter fluid balance and requirements.

Table 2 summarizes our assessment¹² of the likelihood of bias in the reviewed studies. Studies varied in their approach to matching and adjusting for important prognostic variables. Lawrence et al¹¹ matched cases with hospital-based controls within the same treating institution. Edge et al⁹ and Glaser et al¹⁰ matched cases with population-based controls by using demographic data and diabetic history. In addition, Glaser et al¹⁰ matched for the severity of acidosis and hyperglycemia. All 3 studies used multivariate logistic regression in the analysis to

Table 2. Summarizing the assessment of selected studies for susceptibility to important bias.

Assessment	Edge et al, 2006, n=212	Lawrence et al, 2005, n=63	Glaser et al, 2001, n=235
Did the investigators demonstrate similarity with respect to all known risks of outcome and did they adjust for differences in the analysis?	Yes. Matching and adjusted for baseline acidosis in the analysis.	Partially. Matching and used logistical regression models that included a broad range of potential predictors. Adjustment of differences in therapeutic characteristics for differences in severity was limited to BUN value at presentation.	Yes. After confirming that indicators of degree of dehydration and severity of acidosis were associated with cerebral edema, the authors <i>selected</i> a new control group, matched with the cases for age, onset of diabetes, venous pH, and serum glucose concentration at presentation.
Were exposed patients equally likely to be identified in the 2 groups?	Data abstraction was done by a reviewer, who visited hospitals to examine the medical records. The authors do not state whether data abstractors were blinded to clinical outcome or to study hypothesis. Controls were matched within a 6-mo period of the presentation of a case, rendering it unlikely that treatment protocols were different between cases and controls.	Data abstraction was done by a single reviewer, with an investigator cross-checking for accuracy on 3 English-language medical records and a second Francophone reviewer trained by the first reviewer cross-checking 3 French language records. The authors do not state whether the data abstractors were blinded to clinical outcome or to study hypothesis. To control for changes in treatment protocols, controls were taken from the same institution as the case and had to have been treated within 12 mo of the presentation of that case.	A standardized data collection protocol was used; steps were taken to improve interrater reliability in data abstraction from the medical records. The authors do not state whether data abstractors were blinded to clinical outcome or to study hypothesis. However, the authors do not report on whether specific treatment protocols were in place in the target hospitals or whether they changed during the course of the 15-y study period.

Table 3. Comparison of fluid administration between cases (cerebral edema) and controls.

Comparison	Edge et al		Glaser et al		Lawrence et al	
	Cases	Matched Controls	Cases	Matched Controls	Cases	Matched Controls
Number of patients	43	169	61	174	17	28
Fluid Administration	Total infused volume (mL/h)		Rate of infusion of intravenous fluid (per increase of 5 mL/kg of body weight/h)		Rate of infusion of intravenous fluid (mL/kg/h)	
Results	Adjusted odds ratio for large fluid administration during first 4 h: 6.6 (95% CI 1.4 to 31.0)		Adjusted relative risk: 1.1 (95% CI 0.4 to 3.0)		No significant difference using multivariate regression analysis. Adjusted relative risk or odds ratio not reported.	

investigate whether hydration therapy was associated with cerebral edema during the treatment of diabetic ketoacidosis.

Across the included studies, it was not reported that data abstractors were blinded to the identity of the cases and controls. The possibility therefore exists for bias in the data abstraction process with respect to recording the rate or volume of fluids each group received. Finally, the authors of all 3 studies took pains to make sure that apparent associations between fluid administration rates and outcomes between cases and controls were not due to global changes in treatment policy.

In the study by Edge et al,⁹ the investigators discarded a significant proportion of both cases and controls because of misclassification, resulting in a larger than ideal number of unmatched patients. The authors therefore performed a second analysis, using only successfully matched cases, ie, a so-called conditional analysis. Their conditional analysis was restricted to a

smaller subset of patients with complete data sets, which resulted in similar odds ratios with wider confidence intervals (CIs).

RESULTS OF THE TRIALS

Table 3 summarizes the results of the 3 studies included in our review with respect to our principal outcome. Time to develop cerebral edema in the Glaser et al¹⁰ study was a median of 7 hours compared with a median of 5.8 hours in the Lawrence et al¹¹ study, but neither study demonstrated an association between the rate of fluid administration and cerebral edema. Edge et al⁹ showed a significant association for the highest fluid volume range within the first 3 hours (odds ratio 7.3; 95% CI 1.51 to 35.12) and within the first 4 hours (odds ratio 6.55; 95% CI 1.38 to 30.97) when all subjects were included for analysis. Edge et al⁹ also completed a conditional analysis in which incomplete records were removed and found

broadly similar results but with wider CIs. Edge et al⁹ did not match or adjust for BUN in their analysis and, because more severely dehydrated patients are more likely to receive larger fluid volumes, this may partially explain the difference in results between the Edge et al⁹ study and the others.

APPLYING THE EVIDENCE

Returning to the clinical scenario, the child in question with diabetic ketoacidosis appeared severely dehydrated by virtue of pulse rate, decreased capillary refill, and a BUN-to-creatinine ratio of 33. Balancing the low risk of cerebral edema with the degree of dehydration, you decided to continue with an aggressive rehydration scheme. With 10% dehydration, you calculated the replacement intravenous fluid volume to be 2000 mL and the maintenance fluid to be 1500 mL; therefore, after the fluid bolus you initiate a drip of 0.45% saline solution at 135 mL/hour to replenish this deficit during the remaining 23 hours.

All 3 studies demonstrated that cerebral edema was associated with the severity (acidosis and prerenal azotemia) of their initial presentation of diabetic ketoacidosis.⁹⁻¹¹ However, only 1 of them observed a relationship between the volume of fluid administration and the onset of cerebral edema. Do differences in the study design account for the differences in these results?

Selection bias does not account for the differences in the results among the included studies. Although Edge et al⁹ and Lawrence et al¹¹ used a population-based sample and Glaser et al¹⁰ used a hospital-based sample, these differences are unlikely to alter the generalizability of the results because the majority of children with diabetic ketoacidosis, at least in North America, will pass through the hospital ED.

Confounding is a significant problem with the case-control study design. Unlike randomized controlled trials in which known and unknown confounders are equally distributed among the treatment arms, case-control studies attempt to compensate for this deficiency by matching on a few key prognostic factors and then adjusting for other known confounders in the analysis. The study by Edge et al⁹ was the only one of 3 studies to demonstrate an association between higher resuscitation volumes and cerebral edema during the initial treatment of diabetic ketoacidosis. However, Edge et al⁹ measured infused volume without correcting for body weight, as was done in the other 2 studies. If patients developing cerebral edema were heavier relative to their age, the association with fluid administration may be spurious.

Furthermore, a significant proportion of cerebral edema cases (11.6% in Edge et al,⁹ 4.9% in Glaser et al,¹⁰ and 19% in Lawrence et al¹¹) were identified at initial presentation to the hospital, before any intravenous fluid hydration. These observations indicate that the development of cerebral edema in these patients cannot be attributed to the rate or volume of fluid administration and is likely to be multifactorial. Given the inherent limitations of retrospective observational research, strong or consistent evidence implicating fluid administration as a primary cause of cerebral edema after diabetic ketoacidosis is lacking.

PATIENT COMMUNICATIONS

Patients are becoming increasingly more informed about medical interventions and frequently ask about issues of safety and benefit. The following is an example of how an emergency physician might convey what is known about the safety and efficacy of intravenous fluid therapy in treating diabetic ketoacidosis.

“Your child is sick because his diabetes is out of control. This makes his blood sugar very high, which has made him lose a great deal of body fluid and also has made him accumulate acid in his system. Intravenous fluid resuscitation is the standard medical treatment for loss of fluid. There has been controversy about whether this approach should be used for children such as your own. However, the scientific evidence is conflicting, and many, if not most, practitioners are inclined to continue to follow the conventional approach to fluid replacement.”

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

Reprints not available from the authors.

Address for correspondence: Jeffrey Hom, MD, MPH, Department of Emergency Medicine, Box 1228, SUNY–Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203; 718-245-4790, fax 718-245-4799; E-mail jhommdmph@yahoo.com.

REFERENCES

1. Wyer PC, Rowe BH, Guyatt GH, et al. Evidence-based emergency medicine. The clinician and the medical literature: when can we take a shortcut? *Ann Emerg Med.* 2000;36:146-155.
2. Dunger DB, Sperling MA, Acerini CL, et al. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. *Pediatrics.* 2004;113:e133-140.
3. Harris GD, Fiordalisi I, Harris WL, et al. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. *J Pediatr.* 1990;117(1 pt 1):22-31.
4. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5-year prospective pediatric experience in 231 episodes. *Arch Pediatr Adolesc Med.* 1994;148:1046-1052.
5. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr.* 2002;141:793-797.
6. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. *Pediatrics.* 2001;108:735-740.
7. Hale PM, Rezvani I, Braunstein AW, et al. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. *Acta Pediatr.* 1997;86:626-631.
8. Mel JM, Werther GA. Incidence and outcome of diabetic cerebral oedema in childhood: are there predictors? *J Paediatr Child Health.* 1995;31:17-20.

9. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. *Diabetologia*. 2006;49:2002-2009.
10. Glaser N, Barnett P, McClaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001;344:264-269.
11. Lawrence SE, Cummings EA, Gaboury I, et al. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J Pediatr*. 2005;146:688-692.
12. Levine M, Haslam D, Walter S, et al. Harm. In: Guyatt G, Rennie D, eds. *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago, IL: AMA Press; 2002:81-100.

Critically Appraised Topic (CAT): Is fluid administration associated with the development of cerebral edema in children with diabetic ketoacidosis?

Question	Does the administration of intravenous fluid in volumes greater than estimated deficit and maintenance in children with diabetic ketoacidosis progress to cerebral edema?
Reviewed by	Hom J, Sinert RH
Date of search	1966 to January 2007
Expiration date	July 2008
Clinical bottom line	Evidence from the case-control trials lacks any strong or consistent results implicating rate of fluid administration as a precipitant cause of cerebral edema after diabetic ketoacidosis.
Search strategy	MEDLINE, EMBASE, the Cochrane Library from the dates of origin through January 2007
Citations	<p>Primary: 3 case-control trials</p> <ol style="list-style-type: none"> 1. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. <i>Diabetologia</i>. 2006;49:2002-2009. 2. Glaser N, Barnett P, McClaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. <i>N Engl J Med</i>. 2001;344:264-269. 3. Lawrence SE, Cummings EA, Gaboury I, et al. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. <i>J Pediatr</i>. 2005;146:688-692.
Primary study characteristics	<p>Study Population</p> <p>Patients <18 years of age who presented with diabetic ketoacidosis to the ED. Diabetic ketoacidosis is defined by a combination of serum pH, serum bicarbonate, serum glucose, or ketonuria. Cerebral edema is defined by clinical deterioration, radiographic findings, or pathological findings.</p> <p>Cases</p> <p>Children with diabetic ketoacidosis complicated by cerebral edema.</p> <p>Controls</p> <p>Children with diabetic ketoacidosis not developing cerebral edema.</p> <p>Exposure</p> <p>Children who received higher volumes and rates of intravenous fluids.</p>
Critical appraisal	Fair to good quality was observed in all 3 trials.
Results	Primary outcome: cerebral edema
Edge et al	Significant difference in total infused volume (uncorrected by body weight); odds ratio 6.6 (95% CI 1.4–31.0)
Glaser et al	Relative risk: 1.1 (95% CI 0.4–3.0)
Lawrence et al	No significant difference using multivariate regression analysis. Relative risk or odds ratio not reported

APPENDIX E1. SEARCH STRATEGIES USED FOR MEDLINE (PUBMED) AND EMBASE.

PubMed search:

“Brain Edema”[MeSH] AND (“Diabetic Ketoacidosis”[MeSH] OR “Diabetes Complication”[MeSH]); limits: all child, 0-18 years; English, last 3 years

“Time Factors”[MeSH] AND “Brain Edema”[MeSH] AND (“Diabetic Ketoacidosis”[MeSH] OR “Diabetes Complications”[MeSH])-

(“complications”[Subheading] OR “Diabetes Complications”[MeSH] OR “Diabetic Ketoacidosis”[MeSH]) AND “Brain Edema”[MeSH] AND “Time Factors”[MeSH] AND English[Lang] AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms])

“Brain Edema”[MeSH] AND (“Diabetic Ketoacidosis”[MeSH] OR “Diabetes Complications”[MeSH] OR “complications”[Subheading]) AND (“Time Factors”[MeSH] OR “Risk Factors”[MeSH]) AND English[Lang] AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms])

(“Diabetes Complications”[MeSH] OR “complications”[Subheading]) AND “Diabetic Ketoacidosis”[MeSH] AND “Brain Edema”[MeSH] AND English[Lang] AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms]) AND “humans”[MeSH Terms]

(“Diabetes Complications”[MeSH] OR “complications”[Subheading]) AND “Diabetic Ketoacidosis”[MeSH] AND “Brain Edema”[MeSH] AND English[Lang] AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms]) AND “humans”[MeSH Terms]

EMBASE search:

- >1 brain edema.mp. or exp Brain Edema
- >2 diabetic ketoacidosis.mp. or exp Diabetic Ketoacidosis
- >3 diabetes complications.mp.
- >4 exp COMPLICATION/ or complications.mp.
- >5 time factors.mp. or exp Time/
- >6 risk factors.mp. or exp Risk Factor/
- >7 5 or 6
- >8 3 or 4
- >9 2 or 8
- >10 1 and 7 and 9
- >11 from 10 keep 1-85
- >1 brain edema.mp. or exp Brain Edema/
- >2 diabetic ketoacidosis.mp. or exp Diabetic Ketoacidosis/
- >3 diabetes complications.mp.
- >4 exp COMPLICATION/ or complications.mp.
- >5 3 or 4
- >6 1 and 2 and 5
- >7 1 and 2
- >8 from 7 keep 1-194