Supplemental Table 1. Summary of literature examining the role of fluid therapy-related factors in cerebral edema development.

Studies implicating fluid therapy-related factors in CE development		
Descriptive studies		
Article	**Description**	**Findings/Comments**
Clements et al. 1971[114]	5 adults with DKA had CSF pressure monitored during first 10 hours of treatment	Increased CSF pressure developed after rapid drop in BG and decrease in plasma osmolality – all alert on admission, became drowsy during treatment (2 had more severe AMS)
Duck et al. 1976[124]	4 children with moderate-severe DKA and CE evaluated for DKA therapy-related risk factors	All received high fluid volume (> 4 L/m2/day) and had hyponatremia at or near onset of symptoms of CE
Fein et al. 1982[10]	18 children and adults with DKA evaluated with laboratory data; 11 had serial head ultrasound examinations during treatment	Treatment resulted in decreased serum colloid osmotic pressure, hematocrit, and arterial oxygen; 9 of 11 patients had decreased lateral ventricle width and 7 of 9 had hash marks characteristic of CE, which returned to baseline in all
Krane et al. 1985[11]	6 children with DKA examined with head CT scans during treatment and before discharge	Early scans showed narrowing of the ventricles in all 6 (only 2 had lethargy) *Patients received variable fluid volumes and composition
Duck and White 1988[48]	42 children and adults with severe DKA and brain herniation evaluated for risk factors	Rate of fluid administration (> 4 L/m2/day) inversely correlated with onset of herniation; "calculated" serum Na decreased during treatment *17 had stupor/coma before treatment – received more fluid prior to herniation
Hoffman et al. 1988[12]	9 children with DKA had serial head CT scans on admission, during treatment, and 7 days after admission	Both admission and treatment scans showed reduced ventricular sizes compared to 7-day scans; further narrowing between admission and treatment scans occurred in 8 patients (treatment may accentuate subclinical swelling) *Only 1 patient with severe DKA developed clinically apparent CE
Harris et al. 1990[122]	1. 219 episodes of moderate-severe DKA in children and young adults examined for complications and serum Na trends during treatment 2. 58 episodes of moderate-severe DKA in children and young adults examined for serum Na trends while receiving gradual rehydration over 48 hours	1. 20 had complications – serum Na failed to rise as BG declined in 90% of complicated cases; uneven fluid administration with $\leq$ 75 mmol/L Na concentration had higher rates of complications 2. Serum Na rose in 95% of cases and none had major complications *By 24 hours, most cases no longer required IVF
Durr et al. 1992[13]	7 children with DKA/ketosis monitored with laboratory data and head CT scans before, during, and after treatment	At hour 6, CE correlated with rate of change of BG *6 had evidence of CE on CT prior to treatment, but only 1 developed clinical signs of CE at 23 hours; patient without CE only had mild ketosis on admission
Edge and Dunger 1994[123]	25 management protocols from throughout the UK analyzed for variations in treatment regimens in relation to incidence of CE at each center	Centers with CE used higher fluid volumes for resuscitation, suggested larger maintenance fluid volume for children aged 6-9, and were more likely to change to 0.18% NS (vs 0.45% NS) when BG fell
Harris and Fiordalisi 1994[133]	231 consecutive episodes of moderate-severe DKA examined for declines in calculated effective osmolality using gradual rehydration over 48 hours, with initial osmolality approximating that of the patient	90% of episodes exhibited positive serum Na trend in first 12 hours *6 had mild headache and 6 received mannitol for AMS (5 of 6 had positive serum Na trends and all recovered without sequelae) *By 24 hours, 98% of episodes no longer required IVF
Glaser et al. 2006[8]	41 children with DKA evaluated with brain MRI scans during treatment and after recovery	Lateral ventricles narrowed during treatment in 22 children (54%), with higher frequency if imaged later in the treatment course – those with narrowing more commonly had altered mental status (55% vs 21%, p = 0.03)
Fiordalisi et al. 2007[134]	635 cases of DKA in children and young adults treated with new physiologic approach in PICU setting (including gradual replacement of fluid deficit over 48 hours, using rehydration solutions of tonicity approximating that of the patient) evaluated for outcomes	Positive serum Na trend in 91% of patients; negative serum Na trend in remaining patients reversed by decreasing hourly rate of IVF infusion in all but 9% *Mannitol given in 35 cases (5.5%), 74.3% of whom had a preceding positive serum Na trend, and all survived without morbidity (in multiple logistic regression analysis, origination from outside facilities was a risk factor for mannitol administration) – concluded that physiologic treatment approach may minimize risk of brain herniation and positive serum Na trend may be relevant to efficacy of mannitol *Mean time to correction of DKA and complete circulatory restoration occurred over 11.6 ± 6.2 hours
Case-control studies		
Article	**Groups**	**Findings/Comments**
Vlcek 1986[126]	5 pediatric cases of CE within 24 hours of treatment initiation vs 15 random controls with DKA	CE associated with higher fluid volume in first 12 hours and greater fall in BG *CE group also had higher rates of moderate-severe dehydration
Mahoney et al. 1999[37]	9 pediatric cases of brain herniation vs 186 matched (for year of admission, age, and race) controls with DKA	Rate of fluid administration (> 50 mL/kg) during first 4 hours of treatment of severe DKA risk factor for herniation
Edge et al. 2006[49]	UK study of 43 pediatric CE cases vs 169 matched (for age, sex, new/known diabetes, month of admission) controls with DKA	CE associated with higher fluid rate over the first 4 hours (OR 6.55, p < 0.02) when adjusted for age, sex, new/known diabetes, and baseline acidosis
Hoorn et al. 2007[127]	12 pediatric CE cases vs random non-CE DKA controls with hypernatremia (n=44) and without hypernatremia (n=13)	Development of CE associated with drop in effective plasma osmolality during first 8 hours of therapy; CE group received more IVF with more Na and K in first 6 hours, had more positive fluid balance, and higher UOP
Durward et al. 2011[128]	15 pediatric cases with early CE ($\leq$ 1 hour after presentation) and 17 with late CE (1-48 hours after presentation) vs 21 random controls with DKA	Glucose-corrected serum Na and effective osmolality fell in children with late-onset CE and rose in the other 2 groups (both were significant predictors on Cox models when adjusted for blood urea and $PaCO_2$ on presentation); late-onset CE group received more fluid and had lower UOP, with higher net fluid status, in first

		4 hours, but this didn't influence osmolar or glucose-corrected serum Na trajectories in predictable fashion
Tiwari et al. 2012[56]	20 pediatric cases of CE vs 57 random controls with DKA admitted to PICU in India	CE group received more fluid boluses and more fluid volume in first hour *CE incidence high (26%) – patients admitted to PICU were sicker at baseline; presence of fluid refractory shock and azotemia significant predictors of CE on multiple logistic regression analysis
Yaneva et al. 2016[39]	22 pediatric case of CE vs 234 random controls with DKA admitted to PICU in Bulgaria	Initiation of DKA treatment at an outside facility and infusion of higher fluid volume over first 4 hours associated with CE
Agarwal et al. 2020[125]	26 pediatrics cases of CE (22 at presentation, 4 during treatment) vs 85 random controls with moderate-severe DKA admitted to PICU in India	In multivariate regression analysis, prior fluid treatment was the only significant predictor of CE at presentation (OR 4.5, p = 0.013)
Cohort studies		
Article	**Groups**	**Findings/Comments**
Toledo et al. 2009[129]	Comparison of fluids with variable tonicity in 42 pediatric cases of DKA	In multivariate linear regression model, increased Na content of IVF independent variable causing positive tendency toward natremia; accumulated volume/weight had a negative relationship *None had overt CE, but 10 had mild neurologic symptoms (headache, AMS) before treatment and 3 during – could not determine if these correlated with Na content due to small number of cases
Akcan et al. 2019[130]	Comparison of 3 different fluid management regimens with varying rates and NaCl content in 144 children with DKA	CE developed in 18%, lowest in group receiving IVF with highest NaCl content (154 mEq/L) for at least 4-6 hours and constant infusion rate over 48 hours

Studies not directly implicating fluid therapy-related factors in CE development

Descriptive studies

Article	Description	Findings/Comments
Rosenbloom et al. 1980[135]	17 children with CE complicating DKA examined for risk factors	Rate of fluid administration, Na or K infusion, and glucose correction, as well hyponatremia and hypokalemia, not consistent factors in CE development
Rosenbloom 1990[19]	69 cases of intracerebral complications of DKA in children and young adults analyzed for predictive factors	Rate of hydration, tonicity of administered fluid, or rate of correction of glycemia not associated with complications
Smedman et al. 1997[141]	8 children with DKA treated with hypertonic IVF examined with head CT scans ~10 hours after start of treatment, then at 3 weeks to several months later	Only 2 known DM patients with severe DKA had compression of ventricles, but didn't differ in treatment-related measures (i.e., fluid infusion rate) from other patients *No overt CE, only 1 patient briefly complained of headache
Edge et al. 2001[20]	2940 episodes of DKA and 34 cases of CE identified in UK over 3 years (1995-1998)	Risk of CE development 6.8 per 1000 episodes of DKA, similar to rates in US, even though fluid treatments differ between the two regions *CE associated with 24% mortality and 35% morbidity in survivors
Marcin et al. 2002[21]	61 children with CE examined for factors associated with adverse outcomes	In ordinal logistic regression, there was a trend toward association between poor outcomes and lesser rise in serum Na during treatment, but not significant
Jayashree and Singh 2004[142]	68 children with DKA admitted to PICU in India examined for predictors of outcome	CE diagnosed in 9 patients (13%; 2 on admission, initially treated elsewhere); corrected serum Na rose during treatment in CE patients *Higher rate of CE than in Western countries attributed to prolonged duration of illness before diagnosis and inappropriate/inadequate treatment prior to transfer
Hanas et al. 2007[140]	292 cases of DKA in children and young adults in Sweden examined for laboratory parameters at admission and duration treatment	38% of patient had decrease in serum Na during treatment – was not associated with risk of CE development *Subclinical CE in 16 patients, overt CE in 2 (0.68%)
White and Dickson 2013[143]	3712 cases of DKA treated with Dallas protocol (single 20 mL/kg single NS bolus, followed by constant rate of infusion of 3.75 L/m^2/24 h using isotonic fluids with NaCl and K via 3-bag system) assessed for complications	CE diagnosed in only 20 cases (0.5%), 10 treated with intubation and/or mannitol *Dallas protocol gives more IVF, Na, and K in first 24 hours – concluded that it may correct dehydration and restore CNS perfusion faster
Turan et al. 2019[144]	147 episodes of DKA in children and young adults presenting to tertiary care pediatric ED in Turkey examined for effects of pre-hospital care on outcomes	Patients transported by EMS more likely to have severe DKA, receive inappropriate initial fluid type/dose en route, be admitted to the PICU, and develop CE *CE diagnosed in 7.4% of cases (most had moderate/severe DKA) – there was a trend toward association between inappropriate fluid administration by EMS and CE development and the authors concluded that uncorrected hypovolemia may result in complications

Case-control studies

Article	Groups	Findings/Comments
Bello and Sotos 1990[131]	11 children with CE vs 20 random controls with DKA	Decrease in serum osmolality best predictor of CE (OR 17.96, p < 0.001) – in patients with CE, drop in osmolality related to 53% fall in BG and 38% decrease in Na and in controls, 99% of decrease in osmolality related to fall in BG; fluid rate did not differ between the groups *Concluded that CE may have an osmolar cause
Hale et al. 1997[132]	4 children < 5 years with CE vs 10 age-matched controls with DKA, both in context of NODM	Fluid volume and Na content similar in both groups, but mean serum Na and osmolality declined progressively and were consistently lower at 4-hour intervals after the first 4 hours of therapy in children with CE *Concluded that CE may be related to declining serum Na
Glaser et al. 2001[4]	61 children with CE (0.9% of DKA cases) vs random (n=181) and matched (n=174; for age at presentation, new vs established diabetes, and initial BG and pH) controls with DKA	In multivariate regression analysis comparing CE group and matched controls, smaller rise of serum Na during treatment predictive for CE, but rate of BG decrease or IVF or Na infusion not significant predictors

Lawrence et al. 2005[14]	21 pediatric cases of CE (4 at time of diagnosis) vs 42 random controls	In regression analysis, there was a tendency toward association between CE and higher fluid and Na infusion rates, but not significant after Bonferroni adjustment; rate of serum Na or BG change over time didn't differ in the 2 groups
Cohort studies		
Article	**Groups**	**Findings/Comments**
Mel and Werther 1995[136]	Comparison of 2 treatment protocols (rapid rehydration with isotonic fluids [n=3134] vs slow rehydration with hypotonic fluids [n=3373]) over two 10-year periods in children with DKA	CE developed in 12 patients, with no differences between the 2 groups *Adjusted serum Na assessed serially in 6 and fell in each case prior to CE
Felner and White 2001[137]	Comparison of 2 treatment protocols (faster rehydration rate with lower tonicity [n=220] vs slower rehydration rate with higher tonicity [n=300]) over two 2.75-year periods in children with DKA	CE developed in 2 patients with severe DKA, with no differences between the groups
Savaş-Erdeve et al. 2011[138]	Comparison of 2 fluid treatments with different sodium concentrations (75 mEq/L [n=19] vs 100 mEq/L [n=13]) in children with DKA	Changes in BG, serum Na, or effective plasma osmolality (and its nadir) did not differ between the groups; serum Na didn't drop lower than level at diagnosis in both groups *None developed CE
Hsia et al. 2015[139]	Comparison of 2 fluid treatments (faster rehydration rate with lower tonicity [n=604] vs slower rehydration rate with higher tonicity [n=1264]) over two 6-year periods in children with DKA	Incidence of suspected CE (9.6% in faster vs 8.3% in slower rehydration groups), mannitol administration, or adverse outcomes did not differ between groups *CE patients had severe DKA and CE *CE incidence higher if IVF initiated at outside institution
Randomized controlled trials		
Article	**Groups**	**Findings/Comments**
Glaser et al. 2013[73]	18 pediatric DKA cases randomized to 2 IVF regimens (faster [n=8] vs slower [n=10] rehydration, with ~45% difference in fluid infusion rate) and had MRI scans performed 3-6, 9-12, and $\geq$ 72 hours after treatment initiation	Mean ADC values higher during treatment compared to post-recovery, suggestive of a vasogenic process, with no differences between treatment groups; 1 participant in fast hydration group treated for CE (GCS 12) with mannitol
Bakes et al. 2016[145]	50 children with DKA randomized to 2 IVF regimens (higher [n=25] vs lower [n=25] volume infusion)	After adjusting for initial differences in bicarbonate levels by performing post-hoc multivariable Cox proportional hazard regression, higher volume group had hastened time to metabolic normalization (HR 2, $p = 0.04$); none developed CE *Higher volume of infusion may prevent CE by mitigating hypoperfusion
Kuppermann et al. 2018[146]	1389 pediatric DKA cases randomized to 1 of 4 IVF conditions comparing varying fluid rates and Na concentrations and analyzed for neurologic outcomes	No group differences observed in decline in mental status, CE development and short-term memory scores during DKA treatment, or memory and IQ scored 2-6 months after DKA recovery; CE developed in 12 episodes (most presented with severe acidosis and hypocapnia) *On subgroup analysis, those with severe DKA had faster improvement in measures of short-term memory with rapid rehydration *Used fluid rates representing upper and lower boundaries of current protocols for DKA treatment *Those with GCS $\leq$ 11 excluded after year 2

Abbreviations: ADC, apparent diffusion coefficient; AMS, altered mental status; BG, blood glucose; CE, cerebral edema; CSF, cerebrospinal fluid; CT, computed tomography; DKA, diabetic ketoacidosis; ED, emergency department; EMS, emergency medical services; GCS, Glasgow Coma Scale; HR, hazard ratio; ICP, intracranial pressure; IVF, intravenous fluid; NODM, new onset diabetes mellitus; MRI, magnetic resonance imaging; NS, normal saline; OR, odds ratio; UOP, urine output; $PaCO_2$, partial pressure of arterial carbon dioxide; UK, United Kingdom; US, United States.