R E V I E W

Fluid Therapy For Pediatric Patients With Diabetic Ketoacidosis: Current Perspectives

Muralidharan Jayashree [ID]
Vijai Williams [ID]
Rajalakshmi Iyer [ID]

Division of Pediatric Emergency and Intensive Care, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract: Diabetic ketoacidosis (DKA) is a preventable life-threatening complication of type 1 diabetes. Fluids form a crucial component of DKA therapy, goals being the restoration of intravascular, interstitial and intracellular compartments. Hydration reduces hyperglycemia by decreased counter-regulatory hormones, enhanced renal glucose clearance and augmented insulin sensitivity. However, for the last several decades, fluids in DKA have been subject of intense debate owing to their possible role in causation of cerebral edema (CE). Rehydration protocols have been modified to prevent major osmotic shifts, correct electrolyte imbalances and avoid cerebral or pulmonary edema. In DKA, a conservative deficit assumption ranging from 6.5% to 8.5% is preferred. Normal saline (0.9%) has been the traditional fluid of choice, for both, volume resuscitation and deficit replacement in DKA. However, the risk of AKI with its liberal chloride content remains a contentious issue. On the other hand, balanced crystalloids with restricted chloride content need more exploration in children with DKA, both with respect to DKA resolution and AKI. Although fluids are an integral part of DKA management, a fine balance is needed to avoid under-hydration or over-hydration during DKA management. In this narrative review, we discuss the current perspectives on fluids in pediatric DKA.

Keywords: fluids, diabetes, ketoacidosis, pediatrics, children

Introduction

Diabetic ketoacidosis (DKA) is a preventable but serious complication of type 1 diabetes and carries a mortality rate of 0.3–0.5% in developed economies and much higher in developing economies (about 10%).[1,2] It occurs due to an interplay between insulin (deficiency) and counter-regulatory hormones (excess). The former leads to hyperglycemia and ketosis, while the latter (epinephrine, cortisol and growth hormone) released in response to stress, aggravates hyperglycemia by blocking the action of insulin and enhancing glycogenolysis in the liver.[3] When blood glucose levels exceed the renal threshold (180mg/dL), glycosuria occurs. The resultant osmotic diuresis leads to volume depletion and dehydration, which activates the renin-angiotensin-aldosterone axis and also triggers the release of counter-regulatory hormones. These hormones act towards preserving the intravascular volume. Vomiting, due to stimulation of chemoreceptor trigger zone by hydrogen ions and ketones, further aggravates volume loss and dehydration leading to a vicious cycle.

Objectives Of Fluids In DKA

Fluids form a crucial component of DKA therapy, goals being the restoration of the intravascular, interstitial and intracellular volume. An ideal fluid in such a setting

Correspondence: Muralidharan Jayashree
Division of Pediatric Emergency and Intensive Care, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
Tel +91 172 275 5311
Fax +91-172-2744401
Email mjshree@hotmail.com

would be one that causes a predictable and sustained expansion of the intravascular space, has a chemical composition close to that of extracellular fluids, and gets completely metabolized and excreted without any side effects. Hydration causes a decline in counter-regulatory hormones, enhances renal glucose clearance (following improved renal perfusion) and augments insulin sensitivity.[3,4] This, in turn, causes a significant reduction in hyperglycemia, hypertonicity and acidemia. Hydration alone has been shown to reduce glucose concentration by 17–80% over a duration of 12–15 hrs, amounting to an average plasma glucose reduction rate of 25–50 mg/hour.[5,6]

Are Fluids A Double-Edged Sword?

Fluids in DKA have been the subject of intense debate for the last several decades due to their possible role in causation of cerebral edema (CE). Rehydration protocols have been modified to prevent major osmotic shifts, correct electrolyte imbalances and avoid complications of fluid overload like cerebral or pulmonary edema.

Although an uncommon complication of DKA, CE is associated with high morbidity and mortality. Over the years it has become amply clear that its occurrence is multifactorial. Of the several factors implicated, fluids have received the most attention and have been extensively studied.[7–10] Prolonged hyperosmolarity, during evolution of DKA, triggers the formation of intracellular idiogenic osmoles in the brain.[10,11] Slower clearance of these intracellular osmoles, as the serum osmolality declines with hydration, favors movement of water into the brain cells resulting in CE.[11] Volume and tonicity of the fluids used, and rate of correction are important to prevent rapid fall in glucose and osmolality and thereby, CE. However, studies have failed to demonstrate a causal relation between fluid administration and CE.[12–14] Furthermore, the presence of CE before initiation of fluid therapy goes against the theory of fluids being the major culprit.[15] Moreover, despite adopting a conservative approach in fluid therapy, the incidence of CE has remained unchanged over the years again reiterating a fluid independent mechanism for causation of CE.[12,16,17]

The hypoxia-ischemia theory is the alternative mechanism that has been proposed for CE. The risk factors for this theory are related to disease rather than therapy-related factors. These include hypovolemia, acidosis, compensatory respiratory alkalosis and raised blood urea nitrogen.[13] All these factors cause cerebral vasoconstriction leading to cerebral ischemia, hypoxia and increased blood–brain barrier permeability, culminating into CE. Systemic hypoperfusion, secondary to hypovolemia, compromises brain perfusion resulting in loss of cerebral autoregulation and altered co-transport of Na/K/Cl and vasogenic edema. Delayed diagnosis and inadequate fluid repletion only worsen this cascade.

Thus, the pathogenesis of CE follows a "two hit" model. The first hit is "vasogenic edema" related to alterations in blood–brain barrier permeability followed by the second hit, "cytotoxic edema", precipitated by fluids, dysregulation of vasopressin release and sodium bicarbonate administration. Recent report suggests that interleukin 1 released by mononuclear cells on stimulation by high blood glucose may be involved in the pathogenesis of CE.[18]

Although fluids form an integral part of therapy, it is clear that clinicians have to toe a fine line between under-hydration and over-hydration during DKA management. In the light of the above, this review aims to discuss the important evidenced-based aspects of fluid therapy in pediatric DKA. These will include volume and type of fluids, rate of correction, addition of dextrose and complications.

Volume Of Fluids

The volume of fluid to be administered in DKA has three components-

- Bolus volume
- Deficit volume
- Maintenance volume

Bolus fluids

Fluid bolus(es) is/are indicated in children who present in shock (features of poor peripheral perfusion with or without hypotension). Shock however is uncommon in DKA, as intravascular volume tends to be well preserved by the osmotic draw. Therefore, a child with DKA presenting in shock should be suspected to have either severe fluid deficits or complicating sepsis.[19] A high index of suspicion for associated sepsis needs to be entertained especially in malnourished DKA.[19] Children with compensated shock may require volume expansion with 10–20 mL/kg bolus of isotonic saline given over 30–60 mins. Those with hypotensive shock need to be managed as per the Pediatric Advanced Life Support guidelines.[19,20] Requirement of bolus >20 mL/kg in children with DKA is rather uncommon.

Deficit Correction
Deficit Estimation In DKA

Traditionally, children with DKA are assumed to be severely dehydrated, with fluid deficits ranging from 10% to 15%, with a conservative estimate assumed at 10%.[21] However, over the years, increasing concerns of CE, related to over-estimation of fluid deficit and over-zealous fluid administration[7,22] have brought the spotlight on the deficit estimation and its reliability. Studies undertaken to compare the accuracy of clinical estimation of dehydration (the usual practice) with weight-based dehydration assessment (before and after fluid therapy), found that clinical assessment of dehydration was difficult and unreliable. Conventional signs of dehydration like decreased skin turgor, dry oral mucosa, sunken eyes, capillary refill time >2 s and altered neurological status were found to be poor predictors of fluid deficit in DKA.[23] Reduced skin turgor can be absent, as children with DKA tend to have a preserved intravascular volume due to hyperosmolarity. Additionally, the compensatory hyperventilation in response to metabolic acidosis can cause vasoconstriction due to lowering of the vasodilator CO_2 (an indirect effect) thus masquerading as severe dehydration. It is also pertinent to remember that severe acidosis may not always correlate with severe dehydration.[19] Therefore, the assumption of an average overall 10% dehydration in patients with DKA was found to an overestimate. The median absolute measure of dehydration in body water estimation studies was calculated between 5.8% and 8.7%.[23,24] Based on these data, the assumed deficits were reduced to a range of 6.5–8.5% for fluid calculations. DKA is one clinical condition where the "one size fits all" policy seems more appropriate. However, it seems prudent to assume the lower limit (6.5%) in regions where malnutrition is prevalent, to limit the amount of intravenous rehydration in malnourished children[25] as they are likely to have a rapid fall of blood glucose and increased electrolyte imbalances.[26] Deficit volume for replacement is calculated at 6.5% to 8.5% which is equivalent to ([65–85] mL × body weight).

Maintenance Volume

Maintenance fluid volume is calculated as per the Holliday–Segar formula (Table1), which roughly estimates fluid requirement based on weight.

Earlier guidelines had stipulated that all boluses given should be subtracted from the total fluid administered, to avoid over hydration. However, with a more conservative

Table 1 Holliday–Segar Calculation

Weight	Fluid (mL/kg)
<10 kg	100
10–20 kg	1000mL+50
>20 kg	1500mL+20

estimation of deficit assumed at present, this dictum is slightly more controversial. Current recommendations require only boluses beyond 20 mL/kg to be reduced from the total calculated volume of fluid.[20]

$$\text{Total fluid to be administered} = \begin{pmatrix} \text{Deficit volume} \\ +\text{Maintenance} \\ \text{Volume} \end{pmatrix} - \begin{pmatrix} \text{Boluses} \\ 20\text{mL/kg} \end{pmatrix}$$

Rate Of Correction

Rate of fluid correction is also a subject of debate.[12,14] Many centres prefer a slow and even correction spaced over 36–48 hrs, as this has been shown to reduce the risk of CE.[27] The rate of correction is determined by the initial BG levels, serum osmolality, corrected sodium, severity of acidosis, presence of acute kidney injury and depth of altered sensorium. Slower correction is recommended for children with severe DKA and those having very high BG, osmolality and corrected sodium.[7,27]

The recent multi-centric PECARN trial compared faster rate (half of the total calculated volume replaced over 12 hrs, with remaining over 24 hrs; total duration of 36 hrs) with the standard rate of replacement (evenly over 48 hrs). Children with suspected cerebral edema at the outset (GCS < 14) were excluded. The trial investigators found no difference in the incidence of cerebral edema (defined as fall in Glasgow Coma Scale to <14) or time to resolution of DKA in both the groups.[14] The authors' unit prefers slow and even correction over 48 hrs, as the children in their set-up often present late, with severe DKA with or without hyperosmolality.[2]

The total fluid to be administered is calculated for 36–48 hrs and given as hourly infusion. Although several protocols are available (Table 2), with multiple ongoing trials on the type, rate and amount of fluid in DKA, treatment guidelines are still evolving.

Type Of Fluids

Which is the ideal fluid to be used in DKA is a moot question that is arguable or open to debate. Two facets emerge at this juncture – chloride liberal (unbalanced) vs. chloride restrictive (balanced) crystalloids and the optimum tonicity of the fluid (0.9% vs 0.45% saline) to be used.

Table 2 Different DKA Protocols

Protocols	Milwaukee 1988	BSPED 2007 & 2015	ISPAD 2009 & 2014
Fluid to be started	NS	NS	NS
Minimal duration of NS	1 hr	12 hrs at least	4 hrs at least; preferably 12 hrs
Bolus	10–20 mL/kg	10 mL/kg	20 mL/kg only if in shock
Insulin (IU/kg/hr)	0.05–0.1	0.1	0.1
Fluid and insulin	Start together	Start insulin 1 hr after fluids	Start insulin 1–2 hrs after fluids
Duration of correction	23 hrs	48 hrs	48 hrs

Balanced Crystalloids

Normal saline (0.9%) has been the traditional fluid of choice, for both, volume resuscitation and deficit replacement in DKA. However, normal saline may not be as "normal" as one would imagine, as reports of higher risk of acute kidney injury (AKI) and acidosis, related to its chloride content are emerging.[28,29] Proposed mechanisms include renal vasoconstriction leading to reduced cortical tissue perfusion, renal interstitial oedema and intracapsular hypertension. Studies in animals and in healthy human volunteers have postulated that hyperchloremia, by hindering proximal tubular reabsorption of chloride, increases chloride delivery to the distal nephron triggering a negative feedback mechanism that causes reduced GFR, fluid retention and oliguria.[30,31]

Studies in adult surgical patients comparing balanced crystalloids (Ringer's Lactate, Hartmann's solution and Plasma-Lyte) and isotonic saline showed an increased risk of AKI, need for RRT and in some, mortality, in the isotonic saline group.[32,33] The same effect, however, could not be demonstrated in adult RCTs in septic shock or cardiac surgical patients.[34–36] In DKA, a retrospective study by Chua et al in a small cohort of 23 adults, showed that Plasma-Lyte had less hyperchloremia and faster resolution of metabolic acidosis.[37] Subsequently, there have been two RCTs in adults DKA comparing balanced crystalloids with Normal Saline. In the first by Mahler et al, comparing Plasma-Lyte with NS, the former was associated with lower serum chloride and higher bicarbonate levels.[38] In the second by Van Zyl et al, comparing Ringer's lactate with NS, there was no difference in serum creatinine, serum chloride or hospital stay.[39] The only RCT in children comparing balanced fluids with normal saline in 77 children with DKA failed to show any difference in time to resolution of DKA or time to switch to subcutaneous insulin between both groups.[40]

The risk of AKI with chloride liberal fluids still remains a contentious issue. A retrospective analysis from the author's unit showed a significant association between hyperchloremia and AKI, although a causal relationship could not be conclusively drawn.[41] Further studies are necessary to get a final word on the use of balanced crystalloids in DKA. As we await more answers, the current recommendation for volume resuscitation and replacement remains normal saline.

Tonicity Of Fluid: Switch To 0.45% Saline

Isotonic saline used for initial resuscitation may be continued for 4–6 hrs before replacing it with N/2 saline (0.45%). This switch is determined by the serum sodium levels and osmolality. In a resource limited setting, however the non-availability of plain N/2 saline (without dextrose) drives the use of normal saline for a longer duration. The concerns of prolonged normal saline use with respect to hyperchloremia, AKI and cerebral oedema as described above remain unfounded. A recent RCT comparing slower versus rapid fluid administration using either 0.45% saline or 0.9% saline failed to show any significant differences in the frequency of altered mental status or cerebral oedema and long-term neurocognitive outcomes. Although AKI was not one of the studied outcomes in this RCT, there was no difference in blood urea nitrogen values between the 2 groups.[14] In the authors' unit, a switch to 0.45% saline is made after about 4–6 hrs of normal saline therapy, while carefully monitoring serum sodium and osmolality.

Addition Of Dextrose

Rehydration in itself causes partial resolution of hyperglycemia. During the initial phase of volume expansion, blood glucose levels may fall quickly. Subsequently with even correction of volume deficit and insulin therapy, blood glucose is expected to fall at a rate of 50–75mg/dL. A precipitous fall in blood glucose carries the risk of significant osmolar shifts which must be avoided. Additionally, in malnourished children with DKA, the risk of hypoglycemia is

high. Therefore, 5% dextrose is added to the fluids once blood glucose levels reach 250–300 mg/dL (the higher value is selected if there is a rapid fall of blood glucose, or if there is associated malnutrition).[26]

Non-improvement of acidosis in the face of rapidly declining blood glucose sometimes necessitates increment of dextrose up to 10% or even, 12.5%, in order to allow continued insulin use without risk of hypoglycemia. Hypoglycemia should be strictly avoided.[5,19,20]

End Points Of DKA Therapy

Resolution of DKA is not the resolution of hyperglycemia, which may occur much earlier in the course of therapy. Rather, resolution of DKA is the correction of metabolic acidosis and normalisation of bicarbonate levels, closure of the anion gap, and reversion to normal sensorium (Table 3).

Once these end-points are achieved, intravenous fluids are stopped, the child is allowed an oral meal, and the first dose of sub-cutaneous insulin is administered. Insulin infusion is stopped half an hour later. The transition to subcutaneous insulin, with the various types available, is a subject of extensive research, which is out of the scope of this review.

Monitoring During Fluid Therapy

Replacement therapy is guided by clinical and hemodynamic parameters, hydration status, serum electrolyte levels, and urine output, although one must remember that during the early phase of resuscitation, the glycosuria may lead to a spuriously high urine output, making it a poor marker of dehydration. Urinary losses are not routinely replaced during DKA therapy. If any child develops CE during treatment, fluid should be tailored to suit the needs of raised ICP management. Strict assessment of fluid balance is essential in all children.

Fluid Related Complications In DKA
Cerebral Edema

Children have higher incidence of symptomatic cerebral edema as compared to adults, particularly in those with new-onset diabetes. It remains a major complication of

Table 3 End Points Of DKA Therapy

End Points Of Therapy:
• Normal sensorium with good oral tolerance
• Resolution of acidosis pH>7.3 or bicarbonate > 15mmol/L
• Closed anion gap

DKA with a mortality rate of 10–25%.[9,15] The two hit model proposed for cerebral edema has already been explained earlier.

Cerebral edema usually occurs a few hours after the start of DKA therapy with varied symptomatology, ranging from headache to abrupt neurological deterioration and coma. A high index of suspicion is therefore needed in patients with early subtle neurological signs, persistent altered sensorium despite improvement in acidosis (pH>7.3) and hyperglycemia (blood glucose<300 mg/dL). It may be too late to react at the time of profound neurological depression and respiratory arrest.

When cerebral edema is suspected, close monitoring of blood glucose and electrolytes is essential to avoid osmotic disequilibrium. Osmotherapy with mannitol may be used to counter cerebral edema. Fluid volume administered should be curtailed, and other anti-raised ICP measures should be initiated.

Hypokalemia

Hypokalemia in DKA occurs secondary to osmotic polyuria, excretion of potassium along with ketoanions, and due to low potassium stores in malnourished children. Furthermore, during therapy, serum potassium falls as K^+ is driven into the intracellular compartment by insulin and acidosis correction. All children therefore need to be monitored closely with ECG and serial K^+ levels. Suspect hypokalemia in children who have normal or low levels of serum potassium in the presence of severe acidosis. Goal of therapy is to maintain serum potassium between 4 and 5 mEq/L. If the child is hypokalemic at admission, potassium correction should be started immediately by addition of 40mmol/L of potassium to fluids, after ensuring adequate urine output. Administration of insulin may be delayed in severe hypokalemia and may be started after fluid and potassium replacement.

Hypophosphatemia

Hypophosphatemia also results from osmotic polyuria but largely remains asymptomatic. Whole-body phosphate depletion is a hallmark of poorly controlled diabetes. Routine supplementation is not recommended.[42,43] Replacement is indicated in children with anemia, cardiac dysfunction, respiratory depression, muscle weakness or in patients with serum phosphate lower than 1–1.5 mg/dL. One-third of potassium replacement may be administered as potassium phosphate either as intravenous or as phosphate enema. This may offset the chloride load from IV fluids and prevent hypophosphatemia.

Acute Kidney Injury

Acute kidney injury is a common complication encountered during DKA management.[44,45] In a recent retrospective analysis of pediatric DKA, AKI was evident in 30% of admitted children.[44] A retrospective analysis in the authors' unit revealed an AKI incidence of 35% in children with DKA. Elevated chloride levels at 24 hrs predicted the development of AKI, thus suggesting a possible beneficial role of balanced solutions in preventing this morbidity.[41]

Acute Respiratory Distress Syndrome

Non-cardiogenic pulmonary oedema results from reduced colloidal oncotic pressure in pulmonary capillaries due to crystalloid replacements in DKA. Presence of hypoxemia with elevated pulmonary alveolar-arterial gradient, during DKA therapy should warrant suspicion for pulmonary oedema. It can be avoided by judicious fluid replacement.

Hyperchloremic Acidosis

Some children are found to have persistence of metabolic acidosis, despite normalisation of intravascular volume, resolution of ketosis and return to euglycemia. Often this is misconstrued as non-resolution of DKA. This occurs due to conversion of a normochloremic high anion gap acidosis (due to ketonemia) to a hyperchloremic normal anion gap acidosis. This hyperchloremia is attributed to normal saline use during resuscitation and replacement phase of DKA. As mentioned earlier, the hyperchloremia by causing renal injury further hampers the excretion of chloride. Reciprocal loss of bicarbonate ions to maintain electroneutrality results in persistent normal anion gap acidosis. Monitoring for closure of anion gap during DKA therapy will alert the clinician to this phenomenon. This problem settles on its own without any specific intervention.[46]

In conclusion, fluid therapy is the mainstay in the management of DKA. Evidence with respect to fluid type, volume, and rate of therapy is still evolving. Fluids in context of associated comorbidities like malnutrition, sepsis and acute kidney injury also need further exploration. These facets open doors for more multi-centric research. As we await more answers, the current strategy of "one size fits all" with a slow and even correction of fluid deficit may be the best way forward in children with DKA.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2018;67:362–365. doi:10.15585/mmwr.mm6712a3
2. Jayashree M, Singhi S. Diabetic ketoacidosis: predictors of outcome in a pediatric intensive care unit of a developing country. *Pediatr Crit Care Med*. 2004;5:427–433. doi:10.1097/01.PCC.0000137987.74235.5E
3. Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes*. 2009;10 Suppl 12:118–133. doi:10.1111/j.1399-5448.2009.00569.x
4. Inward CD, Chambers TL. Fluid management in diabetic ketoacidosis. *Arch Dis Child*. 2002;86:443–444. doi:10.1136/adc.86.6.443
5. Waldhäusl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. *Diabetes*. 1979;28:577–584. doi:10.2337/diab.28.6.577
6. Nallasamy K, Jayashree M, Singhi S, Bansal A. Low-dose vs standard-dose insulin in pediatric diabetic ketoacidosis: a randomized clinical trial. *JAMA Pediatr*. 2014;168:999–1005. doi:10.1001/jamapediatrics.2014.1211
7. Carlotti AP, Bohn D, Halperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. *Arch Dis Child*. 2003;88:170–173. doi:10.1136/adc.88.2.170
8. 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. doi:10.1007/s00125-006-0363-8
9. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med*. 2001;344:264–269. doi:10.1056/NEJM200101253440404
10. Glaser NS, Wootton-Gorges SL, Marcin JP, et al. Mechanism of cerebral edema in children with diabetic ketoacidosis. *J Pediatr*. 2004;145:164–171. doi:10.1016/j.jpeds.2004.03.045
11. Glaser NS, Ghetti S, Casper TC, Dean JM, Kuppermann N, for the Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study Group. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial: pediatric DKA fluid therapy randomized trial. *Pediatr Diabetes*. 2013;14:435–446. doi:10.1111/pedi.12027.
12. Hsia DS, Tarai SG, Alimi A, Coss-Bu JA, Haymond MW. Fluid management in pediatric patients with DKA and rates of suspected clinical cerebral edema. *Pediatr Diabetes*. 2015;16:338–344. doi:10.1111/pedi.12268
13. Long B, Koyfman A. Emergency medicine myths: cerebral edema in pediatric diabetic ketoacidosis and intravenous fluids. *J Emerg Med*. 2017;53:212–221. doi:10.1016/j.jemermed.2017.03.014
14. Kuppermann N, Ghetti S, Schunk JE, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *N Engl J Med*. 2018;378:2275–2287. doi:10.1056/NEJMoa1716816
15. Tasker RC, Acerini CL. Cerebral edema in children with diabetic ketoacidosis: vasogenic rather than cellular? *Pediatr Diabetes*. 2014;15:261–270. doi:10.1111/pedi.12153
16. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. *Pediatrics*. 2001;108:735–740. doi:10.1542/peds.108.3.735
17. Brown TB. Cerebral oedema in childhood diabetic ketoacidosis: is treatment a factor? *Emerg Med J EMJ*. 2004;21:141–144. doi:10.1136/emj.2002.001578
18. Eisenhut M. In diabetic ketoacidosis brain injury including cerebral oedema and infarction is caused by interleukin-1. *Med Hypotheses*. 2018;121:44–46. doi:10.1016/j.mehy.2018.09.005
19. Zeitler P, Fu J, Tandon N, et al. ISPAD clinical practice consensus guidelines 2014 compendium: type 2 diabetes in the child and adolescent. *Pediatr Diabetes*. 2015;16:392. doi:10.1111/pedi.12239
20. BSPED. Guidelines. n.d. Available from: https://www.bsped.org.uk/clinical-resources/guidelines/. Accessed June 13, 2019.

21. Rosenbloom AL, Hanas R. Diabetic Ketoacidosis (DKA): treatment guidelines. *Clin Pediatr (Phila)*. 1996;35:261–266. doi:10.1177/000992289603500506

22. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990-96. *Arch Dis Child*. 1999;81:318–323. doi:10.1136/adc.81.4.318

23. Koves IH, Neutze J, Donath S, et al. The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. *Diabetes Care*. 2004;27:2485–2487. doi:10.2337/diacare.27.10.2485

24. Ugale J, Mata A, Meert KL, Sarnaik AP. Measured degree of dehydration in children and adolescents with type 1 diabetic ketoacidosis. *Pediatr Crit Care Med*. 2012;13:e103–e107. doi:10.1097/PCC.0b013e3182231493

25. WHO. Paediatric emergency triage, assessment and treatment: care of critically-ill children; n.d. WHO. Available from: http://www.who.int/maternal_child_adolescent/documents/paediatric-emergency-triage-update/en/. Accessed June 13, 2019.

26. Moulik NR, Jayashree M, Singhi S, Bhalla AK, Attri S. Nutritional status and complications in children with diabetic ketoacidosis. *Pediatr Crit Care Med*. 2012;13:e227–e233. doi:10.1097/PCC.0b013e31823c9a11

27. Bohn D, Daneman D. Diabetic ketoacidosis and cerebral edema. *Curr Opin Pediatr*. 2002;14:287–291. doi:10.1097/00008480-200206000-00001

28. Suetrong B, Pisitsak C, Boyd JH, Russell JA, Walley KR. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. *Crit Care*. 2016;20. doi:10.1186/s13054-016-1499-7

29. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- *versus* low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg*. 2015;102:24–36. doi:10.1002/bjs.9651

30. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256:18–24. doi:10.1097/SLA.0b013e318256be72

31. Quilley CP, Lin YS, McGiff JC. Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents. *Br J Pharmacol*. 1993;108:106–110. doi:10.1111/j.1476-5381.1993.tb13447.x

32. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Crit Care Med*. 2014;42:1585–1591. doi:10.1097/CCM.0000000000000305

33. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255:821–829. doi:10.1097/SLA.0b013e31825074f5

34. Young JB, Utter GH, Schermer CR, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg*. 2014;259:255–262. doi:10.1097/SLA.0b013e318295feba

35. Verma B, Luethi N, Cioccari L, et al. A multicentre randomised controlled pilot study of fluid resuscitation with saline or Plasma-Lyte 148 in critically ill patients. *Crit Care Resusc*. 2016;18:205–212.

36. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced Crystalloids versus saline in the intensive care unit. The SALT randomized trial. *Am J Respir Crit Care Med*. 2017;195:1362–1372. doi:10.1164/rccm.201607-1345OC

37. Chua H-R, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care*. 2012;27:138–145. doi:10.1016/j.jcrc.2012.01.007

38. Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *Am J Emerg Med*. 2011;29:670–674. doi:10.1016/j.ajem.2010.02.004

39. Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis–ringer's lactate versus normal saline: a randomized controlled trial. *QJM*. 2012;105:337–343. doi:10.1093/qjmed/hcr226

40. Yung M, Letton G, Keeley S. Controlled trial of Hartmann's solution versus 0.9% saline for diabetic ketoacidosis. *J Paediatr Child Health*. 2017;53:12–17. doi:10.1111/jpc.13436

41. Baalaaji M, Jayashree M, Nallasamy K, Singhi S, Bansal A. Predictors and outcome of acute kidney injury in children with diabetic ketoacidosis. *Indian Pediatr*. 2018;55:311–314. doi:10.1007/s13312-018-1274-8

42. Wilson HK, Keuer SP, Lea AS, Boyd AE, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med* 1982;142:517–20.

43. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab*. 1983;57:177–80. doi:10.1210/jcem-57-1-177

44. Weissbach A, Zur N, Kaplan E, Kadmon G, Gendler Y, Nahum E. Acute kidney injury in critically ill children admitted to the PICU for diabetic ketoacidosis. A retrospective study. *Pediatr Crit Care Med*. 2019;20:e10–4. doi:10.1097/PCC.0000000000001758

45. Parajuli B, Kumar Angurana S, Baalaaji M, Williams V. Acute kidney injury in children with diabetic ketoacidosis: a real concern. *Pediatr Crit Care Med*. 2019;20:590–591. doi:10.1097/PCC.0000000000001928

46. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. *Nephron*. 1990;54:1–6. doi:10.1159/000185800