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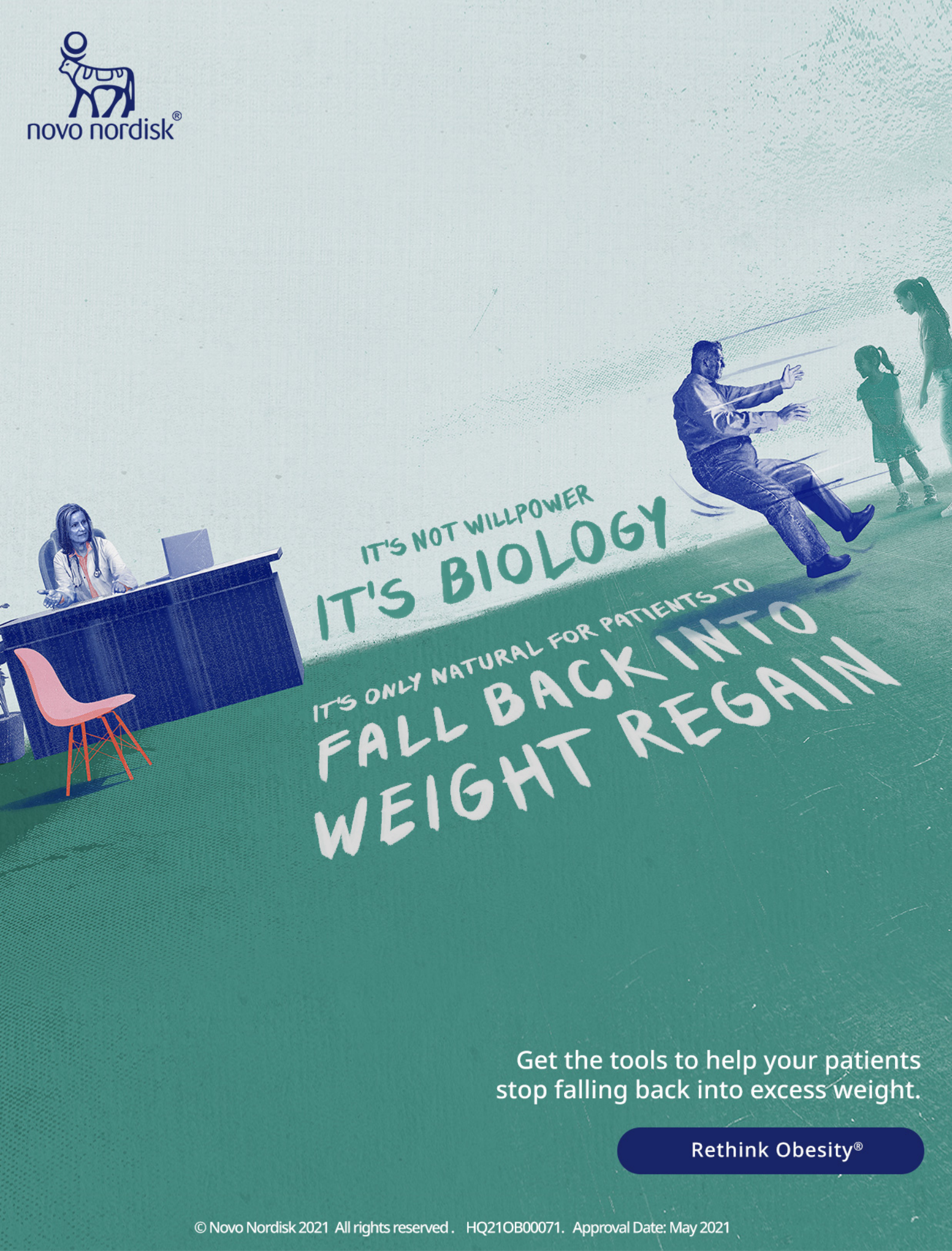

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DIABETIC Medicine

REVIEW

Fluid and electrolyte therapy in childhood diabetic ketoacidosis management: A rationale for new national guideline

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Abstract

Fluid and electrolyte therapy in childhood diabetic ketoacidosis (DKA) management has been controversial. Previous National Institute for Health and Care Excellence (NICE) 2015 guidance advocated a restricted fluid regimen while more recent guidelines have advocated a more liberal approach to fluid replacement in DKA. At the core of the debate is the need to avoid developing cerebral oedema as a complication. Although subtle asymptomatic cerebral oedema is common in children presenting in DKA, clinically apparent cerebral oedema is rare and has been reported in approximately 0.5%–1% of DKA cases in children. Recent research evidence has shown that there was no clear evidence of a difference in rates of clinically apparent cerebral injury in children in DKA managed with a range of fluid volumes and rates of rehydration. In view of this, NICE has updated its guideline. In this paper, we review literature evidence underpinning the current understanding of the pathophysiology of cerebral oedema in children and discuss the rationale for the new NICE guidance.

KEYWORDS

children and adolescents, in-patient diabetes, other complications

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most significant complications of childhood diabetes mellitus, especially in type 1 diabetes. In a UK-wide study between 1990 and 1996, DKA accounted for 75.9% (69/83) deaths in children with type 1 diabetes.[1] 60%–80% of DKA-related death is due to cerebral oedema.[1]

Fluid and electrolyte therapy in childhood DKA management has been controversial. Previous National Institute for Health and Care Excellence (NICE) 2015 guidance advocated a restricted fluid regimen while more recent guidelines have advocated a more liberal approach to fluid replacement in DKA based on new research evidence.[2–4] At the core of the debate is the need to avoid developing cerebral oedema. Although subtle asymptomatic cerebral oedema is common in children presenting in DKA, clinically apparent cerebral oedema is rare and occurs in approximately 0.5%–1% of DKA cases in children.[5–7]

1.1 | Fluid therapy and cerebral oedema

The pathophysiology of cerebral oedema has been a source of scientific debate over the years. In earlier studies, the rate,

volume and tonicity of fluid used in DKA management were implicated in children developing cerebral oedema.[8–10] Duck et al. described four children who developed cerebral oedema, in whom the fluid therapy was given at a rate of more than 4 L/m^2/day during the first 3–15 h of therapy.[8] Others reported that excessive fluid given in the first 4 h was associated with an increased risk of cerebral oedema.[9,10] These and other studies led authors to suggest the osmotic hypothesis to explain cerebral oedema development. It is postulated that hyperglycaemia in DKA leads to a fluid shift from the intracellular fluid (ICF) space to the extracellular fluid (ECF) space, and rapid rehydration with intravenous fluids during DKA management leads to a rapid drop in effective osmolarity, thereby causing a fluid shift from ECF to ICF, leading to brain swelling and cytotoxic cerebral oedema. Many of these early studies, however, either did not have any controls or where controls exist; they were not matched for severity of DKA.[8–10]

Despite changes in DKA management protocols, the prevalence of cerebral oedema has remained stable over the decades.[1,6,7,11] Mel et al. did not show a difference in cerebral oedema frequency after changing protocols for a more conservative regimen.[11] In a population-based study, Lawrence et al. found that 19% of symptomatic cerebral oedema cases had an initial presentation before receiving any medical intervention.[6] Ten of 34 (29.4%) young people with type 1 diabetes who died prior to getting to a hospital in a UK-wide study had evidence of cerebral oedema on post-mortem examination.[1] These findings confirm that intravenous fluid and insulin therapy is not always necessary for patients presenting in DKA to develop cerebral oedema. However, more patients develop cerebral oedema during DKA treatment than before treatment, suggesting that some aspects of DKA treatment may be implicated in cerebral oedema's pathogenesis.

In a retrospective case–control study, Muir et al. reported that 39% of patients diagnosed with cerebral oedema had no radiological abnormalities on their first computerised tomography scan despite having significant neurological symptoms at the time of the scan. Abnormalities consistent with diffuse oedema, haemorrhage and infarction became evident on repeat scans from a few hours to days later.[12] This raises the possibility that cerebral oedema develops later because of cerebral injury rather than being its cause. A magnetic resonance imaging study showed that the children receiving DKA treatment had increased fluid accumulation in the extracellular space (as shown by an increase in apparent diffusion of coefficient values [ADC]) rather than in the intracellular space. This suggests that the mechanism for cerebral oedema is more likely to be a vasogenic process rather than cytotoxic oedema.[13] In that study, the magnitude of the ADC elevation was associated with the severity of dehydration and hypocapnia at presentation. A case-controlled study showed that patients with clinically apparent cerebral oedema were more likely to have a more severe level of dehydration, metabolic acidosis and more severe hyperventilation.[14] These and other studies suggest that the severity of DKA at presentation appears to be a significant risk factor for developing symptomatic cerebral oedema.[6,9,13,14]

What is known about the subject?

- The prevalence of cerebral oedema has remained stable over the decades.
- The previous National Institute for Health and Care Excellence (NICE) 2015 guidance made recommendations for a more restricted fluid regimen due to concerns about cerebral oedema.

What this paper adds

- This paper reviews the most recent evidence and rationale on fluid and electrolyte management in DKA
- NICE 2020 updates on the changes to fluid management of DKA are discussed in line with recent evidence.

These findings led to the hypothesis that cerebral oedema may be due to cerebral ischemia–hypoperfusion and reperfusion injury following DKA therapy. The presence of risk factors such as severe acidosis, hypocapnia and dehydration can lead to a reduction in cerebral blood flow causing, cerebral injury and cytotoxic oedema. However, following therapy and rehydration, the reperfusion of ischemic cerebral tissue causes vasodilation which may impose vasogenic oedema on existing cytotoxic oedema resulting in further cerebral injury.[14] This has raised the possibility that conservative fluid therapies in patients with severe DKA could delay improvement in cerebral perfusion and may be more harmful.

Kupperman et al. reported a recent two-by-two factorial randomised controlled trial (RCT; FLUID trial) in 1255 children (1389 DKA episodes) comparing fast versus slow rehydration with either 0.9% sodium chloride (NaCl) or 0.45% NaCl.[15] Median pH for the cohort at presentation was 7.16 (372 had severe DKA (pH < 7.1) though only 28 had Glasgow coma scale (GCS) < 14 at enrolment. A fluid deficit of 10% was assumed in the fast rehydration group (FRG) and a 5% deficit in the slow rehydration group (SRG). All study patients received an initial 10 ml/kg fluid bolus. In all the arms of the trial, this initial bolus volume was deducted from the total fluid deficit used to calculate the fluid replacement rate. Those randomised to the FRG received an additional 10 ml/kg fluid bolus. In the FRG, half of the total fluid deficit plus maintenance was given in the first 12 h, with the remaining deficit plus maintenance delivered over the subsequent 24 h, while in the SRG, the

total fluid volume was replaced evenly over 48 h after the initial fluid bolus.

There were 12 episodes (0.9%) of clinically apparent cerebral oedema in this study, a rate similar to previous publications.[6,7] The majority (8/12) of patients that developed clinically apparent cerebral oedema in the study had severe DKA at presentation. There was no significant difference between the trial groups in rates of clinically apparent cerebral injury or neurological outcomes ($p = 0.24$, CI 0.15–1.64). Subanalysis of the 372 patients presenting in severe DKA (pH < 7.1) did not show any significant difference in the trial arms in the rates clinically apparent cerebral oedema or decline of GCS below 14; however, some neurological tests (e.g. digit span recall test scores) were significantly better in children in the FRG ($p = 0.03$). The study concluded that neither the rate of rehydration nor sodium composition of the fluid impact the rates of development of either clinically apparent cerebral oedema or development of adverse neurological outcomes. This is the largest study to date on this subject in children and provides robust evidence that the range of fluid rates and volume used in the study protocol can be safely used in DKA management. Notably, there were only 28 children with a GCS of <14 at their presentation with DKA enrolled in the study, so the optimal fluid therapy for this group requires further exploration.

Given this recent evidence, the British Society for Paediatric Endocrinology and Diabetes (BSPED) produced an interim guideline pending publication of the updated NICE guideline.[4] NICE has since updated its guideline in 2020.[16] Table 1 compares key differences between the NICE 2020 guideline, NICE 2015 and the interim BSPED guideline. Table 2 illustrates the difference in fluid replacement a child will receive if the various NICE guidelines or the Fluid regimens used in the FLUID trial were used to calculate fluid requirements. In the remaining paragraphs, we explore the rationale and aspects of fluid and electrolyte management in DKA in the light of the new NICE guideline.

1.2 | Fluid resuscitation

Hyperglycaemia in DKA leads to glycosuria and osmotic diuresis. The combination of insulin deficiency and the resultant volume depletion leads to an increase in counter-regulatory hormones and an increase in glycogenolysis, gluconeogenesis, lipolysis, ketogenesis and reduced glucose utilisation, thereby worsening hyperglycaemia and ketoacidosis. The new NICE guideline advises administering a 10 ml/kg fluid bolus of 0.9%NaCl to children in DKA who appear to be clinically dehydrated. If necessary, a second fluid bolus can be repeated to improve tissue perfusion after careful re-assessment. The fluid bolus is subtracted from the total fluid deficit, and insulin therapy is delayed for at least 1 h. The rationale for the fluid bolus is to promptly improve the circulatory volume and cerebral perfusion; also, fluid therapy reduces the stimulus for the release of counter-regulatory hormones. Waldhäusl et al. showed that glucose levels fall with the initial fluid therapy even before insulin is started.[17] Shock is rare in DKA but can occur in patients who are also septic or severely fluid depleted. Secondary analysis of the FLUID trial showed that only two patients were hypotensive at presentation. Paradoxically, hypertension at presentation was noted in 12.2% (154/1258) of DKA episodes. The aetiology of hypertension at presentation in DKA is unclear.[18]

The new NICE guideline recommends that clinicians should look for evidence of weak, thready (low volume) pulse in the presence of hypotension to diagnose shock. Children with DKA in shock require volume expansion with 20 ml/kg 0.9% saline (which is not subtracted from the total fluid deficit) to restore circulatory status. We conclude that the FLUID trial provides reassurance to clinicians not to withhold fluid resuscitation if clinical signs show a need for volume expansion as restricting fluids may protract the cytotoxic effects of severe dehydration and acidosis. However, there is no evidence to support the use of higher volumes or faster rates than that used in the FLUID study. Children with severe DKA (especially those with GCS < 14) must be closely monitored with early liaison between paediatricians and intensivists.

1.3 | Fluid deficit

Assessment and correction of the fluid deficit are a cornerstone of DKA management; however, this is fraught with problems. The gold standard for assessing dehydration level is the measurement of acute weight changes, but this is often not possible as patients may be too ill to be weighed, and the pre-morbid weight may not be known. In DKA, clinical parameters traditionally used to assess clinical dehydration can be caused by factors other than a fluid deficit. Metabolic acidosis and hypocapnia in DKA can cause vasoconstriction leading to a cool mottled skin appearance, whereas hyperventilation can cause dry oral mucous membrane. Several authors have shown that clinicians typically find it difficult to correctly estimate dehydration in DKA using traditional clinical signs.[19,20] Studies that compared the difference in body weight obtained at the presentation of DKA and at discharge found that most children had 5%–10% weight loss.[19,20] NICE 2020 retained the guidance in the 2015 guideline that clinicians assume 5% dehydration in mild to moderate DKA and 10% dehydration in severe DKA.

TABLE 1 What the different guidelines say about aspects of Fluid and Electrolyte Therapy in DKA; NICE 2020, NICE 2015 and Interim BSPED DKA 2020[2,4,16]

	NICE DKA 2020[16]	Interim BSPED DKA 2020[4]	NICE DKA 2015[2]
Fluid deficit	Mild and Moderate DKA: assume 5% dehydration Severe DKA: assume 10% dehydration	Mild DKA: assume 5% dehydration. Moderate DKA: assume 7% dehydration. Severe DKA: assume 10% dehydration	Same as NICE 2020
Initial bolus administration	Infuse 10 ml/kg 0.9% sodium chloride over 30 min intravenously if clinically dehydrated but not in shock. Deduct bolus fluid from the total fluid deficit. Additional 10 ml/kg bolus fluid can be given after reassessment and discussion with a responsible senior paediatrician	Infuse 10 ml/kg bolus over 60 min to all patients managed with intravenous fluids (not in shock). Deduct bolus fluid from the total fluid deficit	No bolus fluids to those with mild or moderate DKA. No routine bolus fluids to those with severe DKA. Discuss with senior responsible Paediatrician before giving more than one 10 ml/kg bolus
Definition of shock	Shock is defined as weak, thready (low volume) pulse and hypotension	Shock is defined by prolonged central capillary refill, tachycardia, poor peripheral pulses and hypotension (though this is a late sign of shock)	Not defined
Fluid resuscitation during shock	20 ml/kg 0.9% sodium chloride intravenous bolus which is not subtracted from the total fluid deficit	20 ml/kg 0.9% sodium chloride intravenous bolus Following reassessment, further 10 ml/kg boluses (up to a maximum of 40 ml/kg can be given). Fluid boluses should NOT be deducted from the total fluid deficit. Consider the use of inotropes	If the child has received more than 20 ml/kg intravenous fluid bolus, then deduct any additional bolus from the 48-h total fluid calculation
Use of Plasma-Lyte	Not recommended. Calls for more research	Plasma-Lyte 148 recommended as an alternative fluid to 0.9% sodium chloride	No comment
Maintenance fluids	Holliday–Segar formula • 100 ml/kg/day for the first 10 kg of body weight • 50 ml/kg/day for the next 10 kg • 20 ml/kg/day for each additional kilogram above 20 kg • Maximum weight to be used for this calculation is 75 kg	Same as NICE 2020 but maximum weight to be used for calculation is 80 kg	'Reduced volume rules' If the child weighs less than 10 kg: 2 ml/kg/h If the child weighs between 10 and 40 kg: 1 ml/kg/h If the child weighs more than 40 kg: Use a fixed rate of 40 ml/h
Type of fluid for maintenance	Use 0.9% sodium chloride only for fluid resuscitation, then use 0.9% sodium chloride with 20 mmol potassium chloride in 500 ml (or 40 mmol in a litre) without added glucose (unless the patient is anuric or has hyperkalaemia) until the plasma glucose concentration is below 14 mmol/L. Use glucose-containing fluids once plasma glucose drops to less than 14 mmol/L	Use 0.9% sodium chloride with 20 mmol potassium chloride in 500 ml (or 40 mmol in a litre) until blood glucose levels are less than 14 mmol/L. Plasma-Lyte-148 can be used as an alternative but additional potassium will need to be added to the fluid	Similar to NICE 2020
Hyperkalaemia at presentation	Only use fluids containing potassium chloride, if you obtain a history that they have recently passed urine, or their potassium level is less than 5.5 mmol/L	Use potassium-containing fluids only after the patient has passed urine or when their potassium level has fallen to within the upper limit of the normal	Ensure that all fluids (except any initial bolus) administered to children and young people with DKA contain 40 mmol/L potassium chloride, unless they have renal failure

(Continues)

TABLE 1 (Continued)

	NICE DKA 2020[16]	Interim BSPED DKA 2020[4]	NICE DKA 2015[2]
Hypokalaemia	If the child has hypokalaemia at presentation, start potassium replacement before starting insulin therapy. If hypokalaemia develops during treatment, consider suspending insulin infusion temporarily. Discuss care with a critical care specialist if the child requires more than 40 mmol/L intravenous potassium	Same as NICE 2015	No comment on hypokalaemia at presentation. If hypokalaemia develops during treatment, consider suspending insulin infusion temporarily. Discuss care with a critical care specialist if the child requires more than 40 mmol/L intravenous potassium
Care of young people aged 16–18 years	NICE 2020 guideline covers children and young people aged under 18 years old	Local adult guidelines can be used to manage those between ages 16–18 years if teams are not familiar with paediatric guidelines	Same as NICE 2020

1.4 | Maintenance fluid

The current NICE guideline recommends using the Holliday–Segar formula in calculating maintenance fluids.[21] This formula is widely used in general Paediatrics to calculate maintenance fluids and is used in other national and international guidelines for the management of DKA.[3,4] This formula considers both insensible loss and urinary losses based on the child's weight and is the basis of the maintenance fluid calculation used in the FLUID trial.[15] There is no need to replace urinary losses. The total fluid delivered using the Holliday–Segar formula is more generous than that suggested by the 2015 NICE guideline (see Table 2). The 2015 guideline recommended a restricted maintenance fluid regimen, and as such, the total fluid a child would receive using the 2015 guideline is a lot less than either of the arms of the FLUID trial. The concern is that this may be too restrictive and could delay improvement in cerebral perfusion; hence, the recommendation to adopt the same maintenance fluid regimen as used in the FLUID trial.

1.5 | Types of fluids and rate of administration

National Institute for Health and Care Excellence 2020 recommends that the deficit and maintenance fluids be administered evenly over 48 h using 0.9% NaCl saline with potassium supplements. Glucose is added to the fluid when glucose levels fall below 14 mmol/L. This guidance is in keeping with recent evidence showing no difference in clinical outcome between fast and slow rehydration.[15]

The FLUID trial, comparing 0.45% NaCl versus 0.9% NaCl, failed to find a difference in the rate of clinically apparent cerebral oedema or acute kidney injury (AKI); however, hyperchloremic acidosis was more common among those receiving 0.9% NaCl.[15] Hyperchloremic acidosis resolves spontaneously and does not require any specific therapy.

Evidence for the use of other crystalloids in DKA management in children is limited. The only RCT comparing Hartman's solution to 0.9%Nacl as replacement fluid randomised 77 children and failed to find a difference in time for DKA resolution (defined as time to reach a venous $HCO_3 \geq 15$ mmol/L.) or time to change to subcutaneous insulin.[22] A limitation of the study is that non-protocol fluids were allowed making findings difficult to interpret. There is only one study on the use of Plasma-Lyte in the management of childhood DKA. Williams et al. reported an RCT on 64 children (66 episodes of DKA) comparing 0.9% NaCl versus Plasma-Lyte-A as initial fluid.[23] At presentation, over 60% were in severe DKA, and 54.5% had AKI (stages 2 and 3). There was also no difference in the time to resolve DKA or rate of resolution of AKI. Although there was no difference in adverse events, two children in the Plasma-Lyte A group died. This study was undertaken in a setting where children in DKA have higher complication rates than are commonly seen in the UK. There is a need for more research on the use of other crystalloid fluids in childhood DKA management.

1.6 | Potassium

Children in DKA have a total body potassium deficit of about 3–6 mEq/L due to osmotic diuresis, excessive vomiting, volume depletion leading to activation of the renin–angiotensin system, secondary hyperaldosteronism and excessive urinary potassium loss.[24] Insulin deficiency and metabolic acidosis, which is present prior to the start of therapy in DKA, leads to an extracellular shift of potassium, and as a result, potassium levels are rarely low at presentation. However, with insulin initiation, there is a shift of potassium into the intracellular space leading to a drop in serum potassium. If potassium is

TABLE 2 Worked example to illustrate differences in fluid requirements

		NICE DKA 2020	NICE DKA 2015	SRG arm of FLUID Trial	FRG arm of Fluid Trial
10-year-old weighing 30 kg in **moderate** DKA. Child looks dehydrated, but is not in shock	Fluid bolus given	Yes 10 ml/kg (300 ml) with option to repeat	No	Yes 10 ml/kg (300 ml)	Yes 20 ml/kg: 10 ml/kg as initial fluid bolus and another 10 ml/kg as additional fluid bolus
	Total fluid deficit	Fluid deficit (5%) = 1500 ml	Fluid deficit (5%) = 1500 ml	Fluid deficit (5%) = 1500 ml	Fluid deficit (10%) = 3000 ml
	24-h total fluid maintenance	1700 ml	720 ml	1700 ml	1700 ml
	Rate of fluid replacement	After fluid bolus (which is subtracted from total fluid deficit); 96 ml/h evenly over 48 h	61 ml/h evenly over 48 h	After fluid bolus (which is subtracted from total fluid deficit); 96 ml/h evenly over 48 h	After the initial 10 ml/kg fluid bolus is subtracted from total fluid deficit; half the remaining total fluid deficit plus maintenance are replaced in the initial 12 h at rate of 183 ml/h The remaining fluid deficit, plus maintenance fluid is infused during the subsequent 24 h at a rate of 127 ml/h
10-year-old weighing 30 kg in **Severe** DKA. Looks dehydrated but is not in shock	Fluid bolus given	Yes 10 ml/kg (300 ml) with option to repeat	Yes 10 ml/kg (300 ml) with option to repeat	Yes 10 ml/kg (300 ml)	Yes 20 ml/kg (600 ml)
	Total fluid deficit	(10%) = 3000 ml	(10%) = 3000 ml	(5%) = 1500 ml	(10%) = 3000 ml
	24-h total fluid maintenance	1700 ml	720 ml	1700 ml	1700 ml
	Rate of fluid replacement	If child receives only 1 fluid bolus (which is subtracted from total fluid deficit); 127 ml/h evenly over 48 h	If child receives only 1 fluid bolus (which is subtracted from total fluid deficit); 83 ml/h evenly over 48 h	After fluid bolus (which is subtracted from total fluid deficit); 96 ml/h evenly over 48 h	After fluid bolus (which is subtracted from total fluid deficit); half the total fluid deficit plus maintenance are replaced in the initial 12 h at rate of 183 ml/h The remaining fluid deficit, plus maintenance fluid is infused during the subsequent 24 h at a rate of 127 ml/h

Abbreviations: FRG; fast rehydration group; SRG; slow rehydration group.

not replaced, this can lead to severe hypokalaemia, cardiac arrhythmia and possibly death. All the guidelines recommend that maintenance fluids containing potassium are started early, except if the patient is anuric or have hyperkalaemia. The NICE 2020 guideline recommends that clinicians confirm a history that the child has recently passed urine prior to starting potassium-containing fluids.

1.7 | Use of bicarbonate

Metabolic acidosis in DKA is due to a combination of ketoacidosis and lactic acidosis (due to poor tissue perfusion); therefore, fluid and insulin therapy is required to reverse the acidosis rather than the use of bicarbonate. There are no studies showing benefit in children from bicarbonate therapy. A multi-centre case–control study found that children who received bicarbonate therapy were significantly more likely to develop cerebral oedema.[14] Early studies have shown that bicarbonate use can lead to hypokalaemia.[25] All the guidelines advise against the routine use of bicarbonate therapy.

2 | CONCLUSION

Fluid and electrolyte therapy is one of the cornerstones of DKA management. Close monitoring of clinical and biochemical parameters remains very important in the safe management of DKA patients. This paper provides the rationale for the new guidance and highlights key differences with previous guidance to aid clinicians in modifying their local guidelines in line with the current NICE guideline.

CONFLICT OF INTEREST

Juliana Chizo Agwu was the Vice Chair of the NICE Diabetes Update Guideline Development Group for 2020 and Sze May Ng was a committee member in the NICE Diabetes Update Guideline Development Group for 2020.

AUTHOR CONTRIBUTION

All the authors contributed to writing and critically reviewing the manuscript. JCA is the guarantor of the paper. The views expressed in this article are those of the authors and not necessarily those of NICE. The authors have included some references that were not reviewed during development of the NICE 2020 guideline.

DATA AVAILABILITY STATEMENT

There are no data available for sharing.

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