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Fluids in the treatment of diabetic ketoacidosis in children: A systematic review

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Abstract

Aim: To determine the comparative effectiveness of fluid schemes for children with diabetic ketoacidosis (DKA).

Methods: We conducted a systematic review with an attempt to conduct network meta-analysis (NMA). We searched MEDLINE, EMBASE, CENTRAL, Epistemonikos, Virtual Health Library, and gray literature from inception to July 31, 2022. We included randomized controlled trials (RCTs) in children with DKA evaluating any intravenous fluid schemes. We planned to conduct NMA to compare all fluid schemes if heterogeneity was deemed acceptable.

Results: Twelve RCTs were included. Studies were heterogeneous in the population (patients and DKA episodes), interventions with different fluids (saline, Ringer's lactate (RL), and polyelectrolyte solution-PlasmaLyte®), tonicity, volume, and administration systems. We identified 47 outcomes that measured clinical manifestations and metabolic control, including single and composite outcomes and substantial heterogeneity preventing statistical combination. No evidence was found of differences in neurological deterioration (main outcome), but differences were found among interventions in some comparisons to normalize acid-base status (~2 h less with low vs. high volume); time to receive subcutaneous insulin (~1 h less with low vs. high fluid rate); length of stay (~6 h less with RL vs. saline); and resolution of the DKA (~3 h less with two-bag vs. one-bag scheme). However, available evidence is scarce and poor.

Conclusions: There is not enough evidence to determine the best fluid therapy in terms of fluid type, tonicity, volume, or administration time for DKA treatment. There is an urgent need for more RCTs, and the development of a core outcome set on DKA in children.

KEYWORDS
core outcomes set, crystalloid solutions, diabetic ketoacidosis, fluid therapy, infusions, intravenous, neurologic manifestations

1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is children's most frequent endocrine disease. Globally, 542,000 children are diagnosed with T1DM, with an estimated 86,000 new cases yearly.[1,2] Diabetic ketoacidosis (DKA) is one of its main complications, and its incidence varies from 1 to 12 cases per 100 individuals/year.[3–5] DKA is defined as the presence of serum glucose > 200 mg/dL (> 11 mmol/L), pH < 7.3 or serum bicarbonate < 15 mmol/L, and ketonemia or ketonuria.[4] Cerebral edema (CE) occurs in 0.5–1% of DKA patients, with 50–60% mortality rates.[6,7]

Crystalloids are the most frequent intravenous fluids used in managing DKA, especially 0.9% saline solution (0.9% saline). However, given 0.9% saline's supraphysiological sodium content,[9] guideline recommendations on the best fluid vary; some recommend rehydration with 0.9% saline,[8] while others suggest using balanced solutions.[4,7] Balanced solutions, compared to 0.9% saline, contain less sodium and chloride, additional cations and anions, and a composition closer to plasma. Balanced solutions have proven to be superior to 0.9% saline in reducing metabolic acidosis in critically ill adults and children.[9,10,11]

Several RCTs have been conducted in children with DKA. As a result, the most effective and safest fluid and infusion scheme to manage DKA in children remains unknown.[12–14] Therefore, through a systematic review and network meta-analysis (NMA), this work sought to determine the comparative effectiveness—in terms of neurological deterioration and metabolic control—of the fluid schemes used to rehydrate children with DKA.

2 | METHODS

This was a registered (PROSPERO: CRD42020166793) systematic review with attempted network meta-analysis. We followed the PRISMA 2020 statement[15] and the guidelines from the synthesis without meta-analysis (SWiM) guidelines to prepare this report.[16]

2.1 | Eligibility criteria

We included randomized controlled trials (RCTs) evaluating children < 18 years old with DKA who underwent an initial fluid administration. Interventions of interest included any rehydration scheme using any solution (e.g., but not restricted to, 0.9% saline, Ringer's lactate or polyelectrolyte solution), regardless of the administration strategy, including different fluid concentrations, volume, infusion rates, or bag systems compared to each other. We excluded studies including patients with preexisting neurological conditions affecting mental status or those that allowed fluids administration before randomization.

The primary outcomes were neurological deterioration (a decrease in the Glasgow Coma Scale score) and time to recover from neurological deterioration. Secondary outcomes were time needed to correct hyperglycemia (≤200 mg/dL), time to achieve pH ≥7.30, time to achieve bicarbonate ≥15 mmol/L, time to receive subcutaneous insulin, length of stay, incidence of CE, hypoglycemia events, and the total amount of administered fluids.

2.2 | Searches, studies selection, and data extraction

We searched MEDLINE (PubMed), EMBASE, Cochrane Library, Epistemonikos, Virtual Health Library, gray literature, and hand-searches, from database inception until July 31, 2022, without language restriction (Supplementary Material 1). Two authors (DPG, ADL) independently and in duplicate, screened titles, and abstracts, retrieving and reviewing the full texts of abstracts they considered eligible. We included the studies in which both reviewers agreed on their eligibility. Three authors (DPG, ADL, GCB) extracted, independently and in duplicate, the following information: publication details, funding information, characteristics of participants, interventions, comparisons, and outcomes. Three independent authors (DPG, ADL, GCB) evaluated the risk of bias (RoB) using the Cochrane tool 1.0,[17] on our primary outcome or any secondary one, when the former was not available. The RoB was classified as "high," "low," or "unclear." Studies were considered with high RoB when at least one domain was classified as high risk. Disagreements in all the steps were resolved by consensus with other authors (JAC, IDF).

2.3 | Data synthesis

We planned to perform random effects pairwise meta-analyses of available direct comparisons, calculating combined estimates per outcome (risk ratio and mean differences for dichotomous and continuous outcomes) and measuring heterogeneity using the I^2 statistic. We planned to conduct an NMA to provide network estimates by combining direct and indirect evidence. However, due to the scarcity of information, substantial heterogeneity, and the different measures of the outcomes, we could not perform a direct meta-analysis or NMA. Therefore, we summarized narratively the effect estimates for each study per outcome and described all the available outcomes in tables.

3 | RESULTS

3.1 | Studies characteristics

We identified 5616 records, and after removing duplicates, we screened 5136 references, of which 20 were potentially eligible studies. We excluded eight studies (Supplementary Material 2), and included 12 (Figure 1), which are described in detail in Table 1. Figure 2 displays the network plot of the available direct comparisons.

3.2 | Risk of bias

We assessed 11 studies,[14,18–27] as one study was published as an abstract, and we could not obtain the full text.[28]

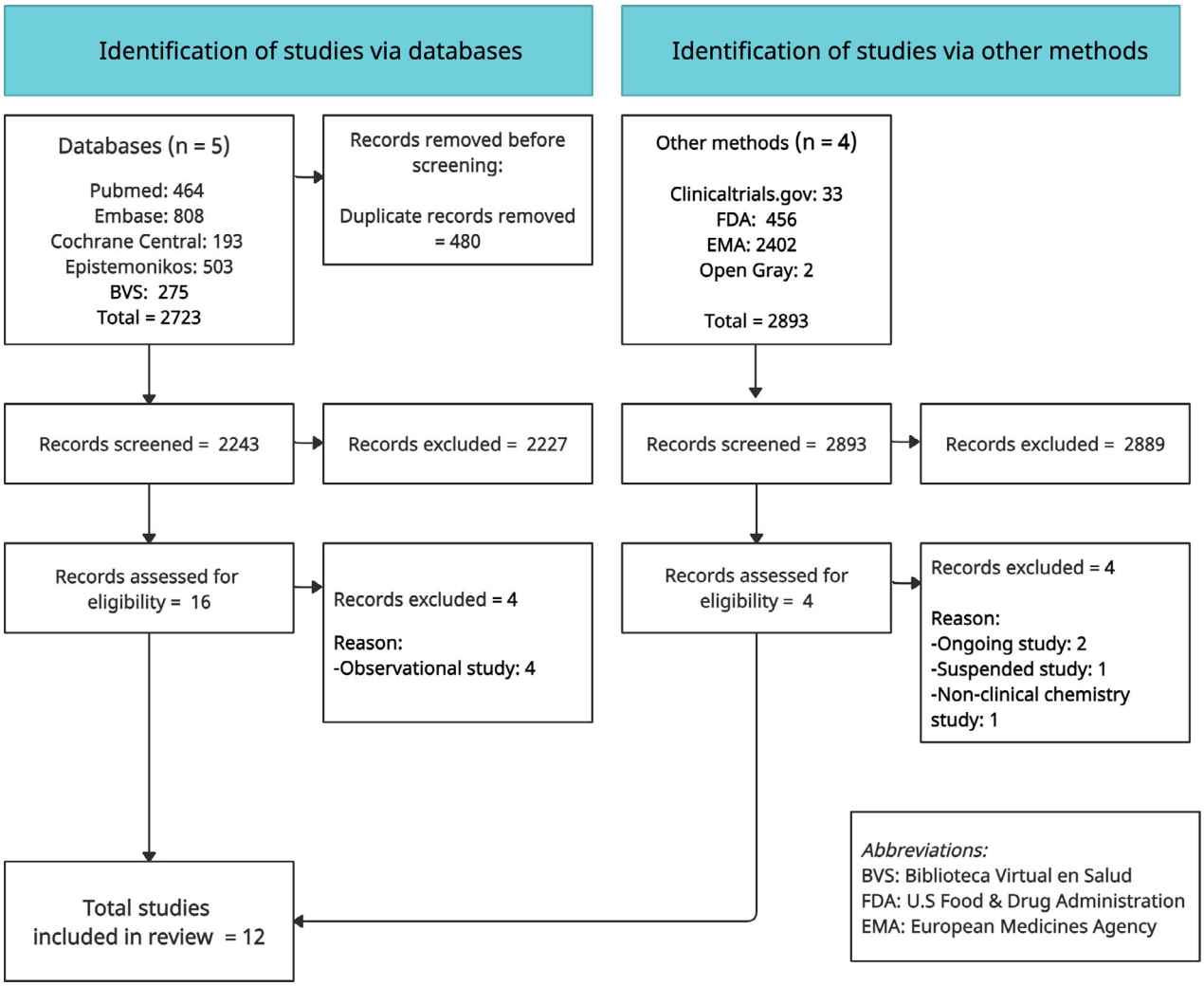

FIGURE 1 PRISMA 2020 flowchart.

Randomization[14,18,19,21–27] and allocation concealment[14,19–23,25–27] methods were adequate in 10 and 9 studies, respectively. There was no blinding of clinicians in eight RCTs,[14,18–21,23,24,26,27] and it was deemed that the outcomes were not likely to be influenced by the lack of blinding in five RCTs.[14,19,20,26,27] Two RCTs were classified as unclear RoB due to incomplete data regarding follow-up,[24,25] and one[24] and three[18,22,23] RCTs were classified as high and unclear RoB, respectively, due to selective reporting. One RCT was classified as having high RoB due to early stopping[20] (Figure 3).

3.3 | Primary outcomes

No studies reported time to recovery from neurological deterioration. Neurological deterioration was reported in three studies.[14,19,26] One RCT compared two protocols using different intravenous fluid bolus and assumed different fluid deficits, different deficit replacement rates, and fluid replacement with 0.9% saline followed by 0.45% saline according to glycemia; one patient in one protocol had neurological deterioration (Glasgow Coma Scale, GCS < 14).[19] The PECARN FLUID trial compared two fast versus two slow fluid administration rate schemes, with 0.45% saline versus 0.9% saline, respectively. Of 1361 DKA episodes evaluated, 3.5% had GCS decline, although no evidence of a difference between interventions was observed.[14] Another study, a secondary analysis of the PECARN study evaluated, found that serum sodium concentration and neurological deterioration events were similar in patients with and without declines in glucose-corrected sodium concentration[26] (Table 2).

3.4 | Secondary outcomes

The time needed to correct hyperglycemia was evaluated by one RCT comparing 3% versus 0.9% saline during the fluid resuscitation phase (first hour of management). The authors did not report differences between groups[24] (Table 2). Four studies[21–23,28] reported the time to achieve pH ≥7.30 and compared: (1) early oral versus intravenous rehydration (without specifying the type of fluid or its concentration);[28] (2) two-bag versus one-bag systems[23]; (3) Ringer's lactate versus 0.9% saline[22]; these three studies observed no

TABLE 1 Characteristics of included studies.

Study	Country	Design	Participants		Intervention		Comparison		Funding
			Age (years)	Sample					
Glaser et al. (2021) (Based on PECARN FLUID trial)	USA	RCT factorial design	4 h: 11 ± 4.4/ 12.1 ± 3.7[a] 8 h: 10.9 ± 4.3/ 12.0 ± 3.8[a] 12 h: 11.1 ± 4.3/ 11.8 ± 4.0[a]	4 h, *n* = 1251 8 h, *n* = 1086 12 h, *n* = 877	Rapid infusion 0.45% saline Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Rapid infusion 0.9% saline Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Slow infusion 0.45% saline Fluid deficit 5%, replacement for 48 h	Slow infusion 0.9% saline Fluid deficit 5%, replacement for 48 h	Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01-HD-062417). Health Resources and Services Administration, Maternal and Child Health Bureau, and Emergency Medical Services for Children.
Rewers et al., (2021) (based on PECARN FLUID trial)	USA	RCT factorial design	12.1 ± 3.9[a]	714 episodes of moderate or severe DKA (667 patients)	Rapid infusion 0.45% saline (*n* = 170) Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Rapid infusion 0.9% saline (*n* = 186) Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Slow infusion 0.45% saline (*n* = 182) Fluid deficit 5%, replacement for 48 h	Slow infusion 0.9% saline (*n* = 176) Fluid deficit 5%, replacement for 48 h	Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01-HD-062417). Health Resources and Services Administration, Maternal and Child Health Bureau, and Emergency Medical Services for Children.
Tej Kola et al. (2020)	India	Open-label RCT	9.78 ± 4.48[a]	40 patients	Oral fluids (*n* = 20)		Intravenous fluids (*n* = 20)		None
Williams et al. (2020)	India	RCT parallel design	7.8 (4.0; 11.6)/6.6 (2.9; 10.1)[b]	66 episodes (64 patients)	PlasmaLyte® (*n* = 34) 48 h maintenance		0.9% saline (*n* = 32) 48 h maintenance		None
Shafi et al. (2018)	India	Open-label RCT	11–18 (42.5%), 6–10 (32.5%) 2–5 (25%)	40 patients	3% saline (*n* = 20) 20 cc/kg during the first hour		0.9% saline (*n* = 20) 20 cc/kg during the first hour		Kalawati Sharan Children's Hospital Lady HArdinge Medical Coll

(Continues)

TABLE 1 (Continued)

Study	Country	Design	Participants		Intervention		Comparison		Funding
			Age (years)	Sample					
Kupperman et al. (2018) (PECARN FLUID trial)	USA	RCT factorial design	11.6 ± 4.07[a]	1389 episodes (1255 patients)	Rapid infusion 0.45% saline ($n = 344$) Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Rapid infusion 0.9% saline ($n = 351$) Fluid deficit 10%, replacement 50% in 12 h and 50% until completing 24 h	Slow infusion 0.45% saline ($n = 345$) Fluid deficit 5%, replacement for 48 h	Slow infusion 0.9% saline ($n = 349$) Fluid deficit 5%, replacement for 48 h	Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Health Resources and Services Administration.
Dhochak et al. (2018)	India	Open-label RCT	7 (3.9; 9.4)/7 (2; 8)[b]	30 patients	Two bags ($n = 15$) Two bags with similar concentration of electrolytes (Sodium 77 mEq/L, chloride 77 mEq/L, potassium 40 mEq/L), one without dextrose and the other with 12.5% dextrose		One bag ($n = 15$) Intravenous fluids with variable concentration of dextrose as needed		None
Bakes et al. (2016)	USA	RCT parallel design	9 (6; 12)/10 (8; 13)[b]	50 patients	High-volume 0.9% saline 20 cc/kg first hour, maintenance 0.675% saline + potassium at 1.5 times maintenance ($n = 25$)		Low-volume 0.9% saline 10 cc/kg first hour, maintenance 0.675% saline + potassium at 1.25 times maintenance ($n = 25$)		None
Yung et al. (2017)	Australia	RCT parallel design	12.9 (11.4; 15.1)/12.4 (8.5; 15.0)[b]	77 patients	Hartmann ($n = 32$) Initial intravenous fluid for at least 12 h		0.9% saline ($n = 39$) Initial intravenous fluid for at least 12 h		None
Ferreira et al. (2015)	Argentina	RCT parallel design	9.2 ± 3.4[a]	12 patients	Two bags ($n = 6$) Two hydro electrolytic solutions with different concentrations of glucose		One bag ($n = 6$) Traditional system		None
Glasser et al. (2013)	USA	RCT parallel design	11.5 (9; 14)/15 (9; 18)[b]	18 episodes	Protocol A ($n = 8$) 0.9% saline bolus 20 cc/kg, deficit 10%, 2/3 in the first 24 h and 1/3 to complete 48 h		Protocol B ($n = 10$) 0.9% saline bolus 10 cc/kg, deficit 7%, for 48 h		None
Poirier et al. (2004)	USA	Prospective clinical trial	11.2 ± 4.7/14.1 ± 2.2[a]	33 patients	Two bags ($n = 17$) Two hydro electrolytic solutions with different concentrations of glucose		One bag ($n = 16$) Traditional system		None

Abbreviations: DKA, diabetic ketoacidosis; mEq/L, milliequivalents per liter; RCT, randomized controlled trial.

[a]Mean ± SD.

[b]Median (IQR).

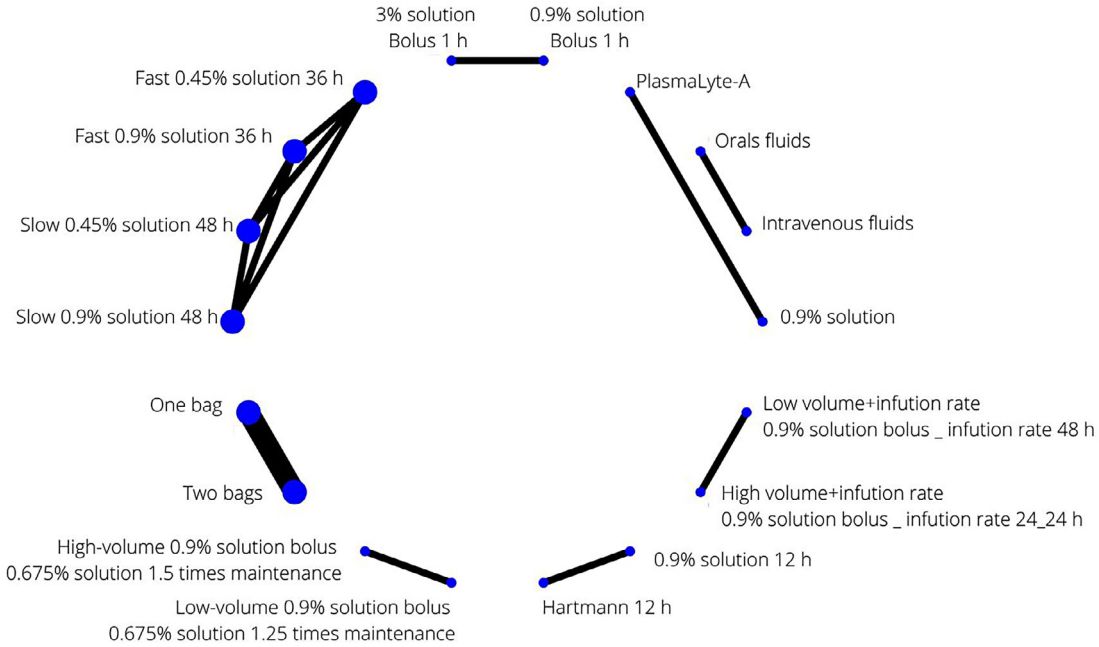

FIGURE 2 Network plot of the available direct comparison among different fluids schemes.

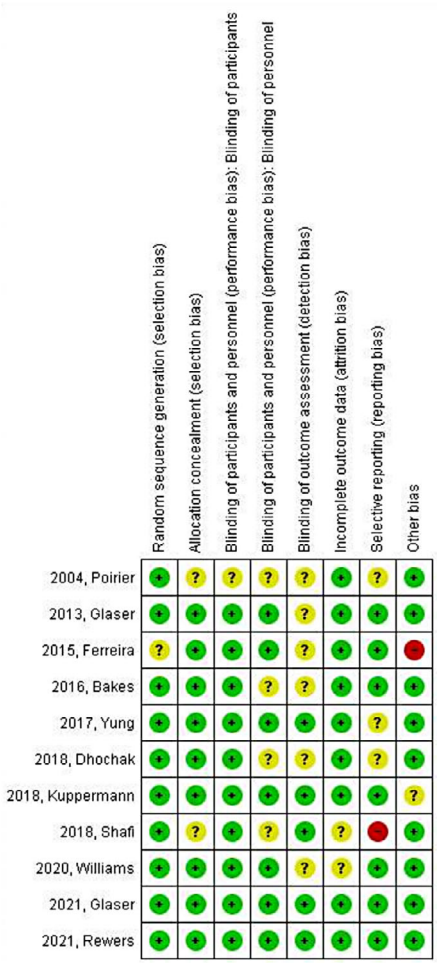

FIGURE 3 Risk of bias of included studies.

differences among the interventions; and (4) higher (20 mL/kg 0.9% saline) versus lower infusion volume (10 mL/kg 0.9% saline) during resuscitation and maintenance (0.675% saline + potassium replacement at 1.5 times versus 0.675% saline + potassium replacement at 1.25 times)[21] while this last one reported a longer time to achieve pH ≥7.30 in the higher infusion volume group[21] (Table 2).

Time to achieve bicarbonate ≥15 mmol/L was reported by two studies,[21,22] comparing Ringer's lactate versus 0.9% saline[22] and higher volume versus lower volume during resuscitation (20 mL/kg vs. 10 mL/kg with 0.9% saline).[21] Both studies showed no differences between the groups (Table 2).

Time to receive subcutaneous insulin was reported by two studies.[22,27] A secondary analysis[27] of the PECARN study[14] compared rapid versus slow infusion speeds and 0.45% saline versus 0.9% saline; the time to receive subcutaneous insulin was longer with the rapid infusion. The second study compared Ringer's lactate versus 0.9% saline and found no differences between them[22] (Table 2).

Length of hospital stay was reported by four studies.[21,22,25,28] One RCT found a shorter stay in PICU or high-dependency units in the Ringer's lactate group compared with 0.9% saline.[22] The remaining studies reported no evidence of differences among interventions.[21,25,28]

Cerebral edema (CE) was reported by three studies,[21,23,24] comparing 3% versus 0.9% saline during the resuscitation phase, two bags versus one bag, and higher versus lower volume. The incidence of hypoglycemia was evaluated only by one RCT, which found a similar number of episodes in both interventions (two vs. one bag).[23] Finally, none of the studies reported the total amount of fluids administered (Table 2).

TABLE 2 Description of outcomes.

Primary outcomes						
Outcome	**Study**	**Evaluated aspect**	**Intervention**	**Comparation**	**Effect's magnitude**	**Conclusion**
Neurological deterioration (GCS < 14)	Glasser et al. (2013)	Infusion rate and volume	Fast/high volume	Low/low volume	One patient decline in GCS (Intervention)	No differences
	Kupperman et al. (2018)	Infusion rate	Fast	Low	RR 0.76 (IC 95%: 0.44–1.33)	No differences
		Tonicity	0.45% saline	0.9% saline	RR 0.80 (IC 95%: 0.46–1.40)	
	Glaser et al. (2021) (Based on PECARN FLUID trial)	Glucose-corrected sodium concentration	Stable or increased	Decreased	4 h, 17 (3.2%) vs. 21 (2.9%) 8 h, 17 (3.9%) vs. 20 (3.2%) 12 h, 18 (4.9%) vs. 16 (3.3%)	No differences
Time until recovery of neurologic status	None	-	–	–	–	–
Secondary outcomes						
Outcome	Study	Evaluated aspect	Intervention	Comparation	Effect's magnitude	Conclusion
Time needed for the correction of hyperglycemia	Shafi et al. (2018)	Tonicity	3% saline	0.9% saline	7.13 vs. 7.15 h	No differences
Time to achieve pH ≥7.30	Tej Kola et al. (2020)	Hydration pathway	Oral	Intravenous	14.7 ± 6.9 vs. 16.4 ± 8.9 h	No differences
	Dhochak et al. (2018)	System of administration	Two bags	One bag	20.3 ± 7.0 vs. 20.3 ± 14.8 h	No differences
	Yung et al. (2017)	Type of fluids	Hartmann	0.9% saline	7.5 ± 1.8 vs. 8.5 ± 2.8 h	No differences
	Bakes et al. (2016)	Volume	High volume	Low volume	HR 2.5 (IC 95%: 1.2–5.0)	Approximately 2 h more
Time to achieve bicarbonate ≥15 mmol/L	Yung et al. (2017)	Type of fluids	Hartmann	0.9% saline	6.2 ± 4.7 vs. 8.6 ± 2.3 h	No differences
	Bakes et al. (2016)	Volume	High volume	Low volume	HR 1.2 (IC 95%: 0.6–2.3)	No differences
Time to receive subcutaneous insulin	Rewers et al. (2020)	Infusion rate	Fast	Low	8.8 ± 5.3 vs. 7.6 ± 4.8 h	Approximately 1 h more
		Tonicity	0.45% saline	0.9% saline	8.8 ± 5.3 vs. 8.2 ± 4.5 h	No differences
	Yung et al. (2017)	Type of fluids	Hartmann	0.9% saline	14.3 ± 1.6 vs. 15.2 ± 2.4 h; HR 1.1 (IC 95%: 0.8–1.5)	No differences

(Continues)

TABLE 2 (Continued)

Primary outcomes						
Outcome	**Study**	**Evaluated aspect**	**Intervention**	**Comparation**	**Effect's magnitude**	**Conclusion**
Overall length of stay	Tej Kola et al. (2020)	Hydration pathway	Oral	Intravenous	No available	Similar in both groups
	Williams et al. (2020)	Type of fluids	PlasmaLyte®	0.9% saline	48 (48, 60) vs. 47 (24, 54) h[b]	No differences
	Yung et al. (2017)	Type of fluids	Hartmann	0.9% saline	17.3 (14.0, 23.3) vs. 23.8 (15.8, 26.4) h[b]	Approximately 6 h less
	Bakes et al. (2016)	Volume	High volume	Low volume	HR 0.82 (IC 95%: 0.44–1.54)	No differences
Cerebral edema	Shafi et al. (2018)	Tonicity	3% saline	0.9% saline	4 vs. 6 h	No differences
	Dhochak et al. (2018)	System of administration	Two bags	One bag	None	None
	Bakes et al. (2016)	Volume	High volume	Low volume	None	None
	Poirier et al. (2004)	System of administration	Two bags	One bag	None	None
Total amount of administered fluids	None	–	–	–	–	–
Incidence of hypoglycemia	Dhochak et al. (2018)	System of administration	Two bags	One bag	4 (26.7%) vs. 6 (42.9%)	No differences
Other outcomes						
Outcome	Study	Evaluated aspect	Intervention	Comparation	Effect estimate magnitude	Conclusion
Time to DKA resolution (composite outcome)	Williams et al. (2020)	Type of fluids	Plasmalyte®	0.9% saline	14.5 (12, 20) vs. 16 (8, 20) h[b]	No differences
	Shafi et al. (2018)	Tonicity	3% saline	0.9% saline	18 vs. 17.3 h	No differences
	Bakes et al. (2016)	Volume	High volume	Low volume	HR: 2.0 (IC 95%: 1.0–3.9)	No differences
	Ferreira et al. (2015)	System of administration	Two bags	One bag	9.8 ± 1.1 vs. 13.3 ± 2.8 h	Approximately 3 h less; study suspended before of the finalization

Abbreviations: DKA, diabetic ketoacidosis; GCS, Glasgow Coma Scale; HR, hazard ratio; IQR, interquartile range; SD, standard deviation.
[a]Mean ± SD.
[b]median (IQR).

TABLE 3 Outcomes evaluated in the included studies and other outcomes.

	Outcomes from our review										Other outcomes from the studies	
	Primary					Secondary						
Studies	O1	O2	O3	O4	O5	O6	O7	O8	O9	O10	Primary	Secondary
Glaser et al. (2021)	■										(36)	(16)
Rewers et al. (2021)						■					(1)	(2)
Tej Kola et al. (2020)				■			■				(3)	(4), (5), (6)
Williams et al. (2020)							■				(7)	(4), (8), (9), (10), (11), (12)
Shafi et al. (2018)			■					■			(9), (13), (14)	
Kupperman et al. (2018)	■										(15)	(14), (16), (17), (18), (38)
Dhochak et al. (2018)				■				■		■	(19)	(9), (14), (20), (21)
Bakes et al. (2016)				■	■		■	■			(9)	(4), (5), (22), (23)
Yung et al. (2017)				■	■	■	■				(9)	(5), (24), (25), (26), (27), (4), (28)
Ferreira et al. (2015)											(9)	
Glaser et al. (2013)	■										(14)	(29), (30)
Poirier et al. (2004)								■			(29)	(15), (26), (31), (32), (33), (34), (35)

Outcomes from our review: O1, neurological deterioration; O2, time to recovery of neurological status; O3, time needed to correct hyperglycemia; O4, time to achieve pH ≥7.30; O5, time to achieve bicarbonate ≥15 mmol/L; O6, time to receive subcutaneous insulin; O7, overall length of stay; O8, cerebral edema; O9, total amount of fluids administered; O10, incidence of hypoglycemia.

Other outcomes from the studies: (1) rates of change in pH, PCO2, anion gap, glucose, glucose-corrected sodium, chloride, and potassium during treatment, (2) rates of adverse events related to changes in glucose and electrolytes (hyperchloremic acidosis and hypernatremia), (3) efficacy of oral vs. intravenous fluid (IV) therapy in correction of dehydration in DKA (pH ≥ 7.25), (4) length of stay per service, e.g., ICU, (5) time to normalization pH, (6) time to improvement of hyperchloremic acidosis, (7) incidence of new onset or progressive Acute Kidney Injury, (8) rate of resolution of AKI, (9) time to resolution of DKA, (10) change in chloride, pH and bicarbonate levels (baseline, 24 h), (11) proportion in-hospital all-cause mortality, (12) proportion of children requiring renal replacement therapy, (13) changes in heart rate, blood pressure, respiratory rate, sodium levels, chloride levels, lactate, pH and blood sugar at 1, 2, 4, 6, 12, 24 and 48 h, (14) cerebral edema, (15) confirmed decline in Glasgow Coma Scale score to < 14, (16) short-term memory (digit-span recall test, forward slope), (17) digit-span recall test, backward slope, (18) IQ 2 to 6 months after the episode of diabetic, (19) blood glucose variability, defined as number of episodes of undesirable BG change (hourly BG change (either increase or decrease > or = 50 mg/dL)), (20) episodes of hypoglycemia (BG < 50 mg/dL), (21) hypokalemia (serum potassium < 3.5), (22) time to bicarbonate normalization, (23) development of adverse outcomes, (24) time to commence SC insulin, (25) time to commence oral intake other than water, (26) time to change in fluid type, (27) total insulin requirement per kg, (28) time to normalization (< 16.1 mmol/L) of anion gap, (29) brain NAA/creatine ratio & brain lactate measured by MR spectroscopy, cerebral blood flow & oxygen saturation measured by MR perfusion weighted imaging & near infrared spectroscopy, (30) mental status evaluated by Glasgow Coma Scale Scores, (31) rate of decline in serum glucose in mg/dL, (32) rate of serum bicarbonate correction in mEq/h, (33) total time on IV insulin therapy, (34) response time for changes in IV fluid glucose concentration and rate, (35) total number of IV bags used, (36) glucose-corrected sodium concentration.

3.5 | Summary of reported outcomes

The included trials reported 36 additional outcomes apart from our prespecified outcomes of interests, including some of the composite outcomes. Namely, in total, 46 outcomes have been reported in DKA fluid trials. This heterogeneity in the measurement of the outcomes is detailed in Table 3. None of the studies reported the time to recovery of neurological status or the time to resolution of DKA and the most common outcomes across the trials were: time to achieve pH ≥7.30, overall length of stay, and CE that were measured by four studies each.

4 | DISCUSSION

This systematic review sought to evaluate differences in the clinical deterioration and metabolic control among different fluids in DKA. However, we found substantial heterogeneity in population, interventions, and outcomes measurement, preventing us from conducting the planned statistical pooling. Thus, we could only descriptively summarize the results. Most of the studies showed that they were of low risk.

4.1 | Types of fluids

Two studies compared balanced solutions (polyelectrolyte solution[25] and Ringer's lactate[22]) with 0.9% saline, with one finding a shorter length of hospital stay with Ringer's lactate[22] without evidence of differences in metabolic outcomes.[29] Guidelines for DKA management recommend 0.9% saline as the first-line fluid due to its low cost and widespread availability.[4,7] However, 0.9% saline contains supraphysiological levels of sodium and chloride (154 mmol/L each, and no electrolytes), and it has been associated with metabolic acidosis, longer hospitalizations, and acute renal injury.[9,30,31]

The alternative to 0.9% saline is the balanced solution (Ringer's lactate and polyelectrolyte solution), which contains less sodium and less

chloride and contains additional cations, (calcium, potassium, and magnesium), and buffer anions (lactate, acetate, and gluconate); therefore, hyperchloremic acidosis is less likely to occur.[7,31,32] Although robust evidence in DKA is lacking, balanced solutions might be reasonable alternatives to 0.9% saline to rehydrate children with DKA. Unfortunately, we could not evaluate the potential differences between balanced solutions and 0.9% saline.

4.2 | Tonicity

The tonicity of saline solutions (i.e., 0.9%, 0.45%, 0.675%, and 3%) has been studied for DKA treatment. However, studies found no evidence of differences in neurologic and metabolic outcomes associated with them.[14,24,26,27] Tonicity corresponds to the effective osmolarity, or the net force of water movement across the cell membrane, based on the osmotic pressure determined by the sodium content.[33] In recent decades, fluids in DKA have been debated as their inappropriate use could lead to the development or worsening of CE associated with tonicity or the rate of fluid administration.[4,32,34]

4.3 | Infusion rate and volume

Cerebral injuries occur in 0.5%–0.9% of episodes of DKA in children,[14,35] and CE is the most feared complication. CE is associated with excessive rates of fluid infusion, mainly when associated with rapid declines in serum osmolality. According to this hypothesis, CE should be reduced by administering fluids at slower rates.[36,37] In this review, three studies reported on administration rates (fast vs. slow),[14,19,26] and two reported on the volume (high vs. low)[19,21] without differences in neurological deterioration rates. One study reported a longer time to initiation of subcutaneous insulin therapy with a fast infusion,[27] another found a longer time to achieve pH ≥7.30 with higher volume,[21] and another reported higher glucose-corrected sodium concentrations at 12 h with fast infusion.[26]

4.4 | Administration system

The one-bag system consists of an initial administration of a fluid with electrolytes and subsequent administration of dextrose to prevent hypoglycemia. This approach has been associated with slow response times and increased hospital costs.[38,39] Meanwhile, the two-bag system consists of one bag with the fluid with electrolytes and another with a fixed dextrose concentration (e.g., 10% or 12.5%). By adjusting the administration rates of each bag individually, we provide different concentrations of glucose while keeping a constant final fluid delivery. Some advantages of this system are a faster fluid rate of change, fewer intravenous fluid bags and, therefore, a potential reduction in related costs. Although no differences were found between the two-bag and the single-bag system in terms of clinical outcomes,[18,20,23] one study reported a faster time to resolution of the DKA with the two-bag system.[20]

Although the evidence is scarce and rather poor, no evidence of differences in neurological deterioration with varying saline tonicity, infusion rate, or volume was found.[40] The schemes that show differences in some outcomes indicate that low volumes and slow rates of 0.9% saline may be superior to high volumes and fast rates, respectively; Ringer's lactate may also be superior to 0.9% saline in terms of PICU length of stay; and the two-bag system may be superior to the one-bag system. However, these differences were found in secondary outcomes, and further studies were needed to confirm them.[14,19,21,26,27]

4.5 | Heterogeneity and the need for core outcomes set

As mentioned, the studies were highly heterogeneous. In terms of population, the unit of analysis was, in some studies, the number of patients,[19,21,22,24,28] while in others, the number of DKA episodes.[14,25–27] Interventions could not be grouped due to varied tonicities and uses of different solutions and volumes for boluses.[14,18–21,24,25,27] Moreover, maintenance volume replacement was calculated with different percentages of the estimated water deficit.[14,18,19,22,24] With respect to infusion rates, slow and fast infusion schedules for 24, 36, 48, and 72 h or until the patient's stability was achieved were evaluated.[14,19,22,24] Lastly, three studies evaluated the double-bag system.[18,20,23]

Nonetheless, the heterogeneity in the outcomes measured concerns us the most. We planned to measure ten outcomes and found that studies reported 36 additional ones. Using very different outcomes to measure effectiveness and safety in studies addressing the same clinical question may negatively affect the development of clinical trials, systematic reviews, and clinical practice guidelines.[41,42] Moreover, practical recommendations produced by guidelines will differ if a lack of consensus exists on the best outcomes to measure.[4,7,8] The development of core outcome sets (COS) may solve this problem;[43] COS could standardize the best outcomes to measure and report as a minimum in RCTs in children with DKA.[41,44,45] The benefits include reducing heterogeneity, reporting bias, and involving people to identify clinically relevant outcomes without affecting innovation in research.[41,44,45] COS have been developed for pediatric diseases such as diarrhea, bronchiolitis, and autism, among others.[46] Our study highlights how the lack of consensus on the DKA outcomes affects evidence generation; thus, COS should be a priority in this field.

4.6 | Strengths and limitations

This study has several strengths. We followed the Cochrane handbook to guide the conduction and the recommendations for reporting evidence syntheses studies without meta-analysis.[16] Also, our methods were prespecified in our registered protocol. There are also some

limitations to describe; the high heterogeneity prevented us from conducting an NMA.[47] The lack of agreement on the best trial outcomes affects these syntheses and the development of guidance to support clinical decisions. Finally, additional factors not explicitly mentioned in the studies, such as comorbidities and time to receive subcutaneous insulin, among others, may have impacted the results. One study could not be evaluated because it was published as an abstract.[28]

4.7 | Conclusions

Our review could not determine the best rehydration scheme regarding fluid type, tonicity, volume, or infusion rate for managing DKA in children. Very scarce evidence suggests that low volumes and slow rates might be superior to high and fast rates, Ringer's lactate might be superior to 0.9% saline, and the two-bag system may be superior to the one-bag system. Available RCTs have significant heterogeneity in the population, intervention, and outcomes, preventing us from a statistical combination. Our findings support further efforts to develop a COS for DKA in children.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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